DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS

ADVISORY COMMITTEE

Monday, March 23, 2006

8:00 a.m.

Hilton Hotel
The Ballrooms
Gaithersburg, MD

PARTICIPANTS

Wayne K. Goodman, M.D., Chair
Cicely Reese, Pharm.D., Executive Secretary

COMMITTEE MEMBERS:

Jorge Armenteros, M.D.
Jean Bronstein, R.N., M.S.
Andrew C. Leon, M.D.
Daniel S. Pine, M.D.
Delbert Robinson, M.D.
Philip Wang, M.D., Dr.P.H.
Barbara Wells, Pharm.D.

TEMPORARY VOTING MEMBERS:

Michael Bigby, M.D.
Deborah Dokken, MPA
Richard Malone, M.D.
Cynthia Pfeffer, M.D.
Marsha Rappley, M.D.

NON-VOTING MEMBER:

Dilip Mehta, M.D., Ph.D.

FDA PARTICIPANTS:

Robert Temple, M.D.
Thomas P. Laughren, M.D.
Paul J. Andreason, M.D.
Glenn Mannheim, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. GOODMAN: We expect a few more people to join us around the table but I want to make sure that we start on time. Welcome, everyone, to the Psychopharmacologic Drugs Advisory Committee, or the PDAC. We have been asked today by the FDA to advise them on a new drug application for modafinil in the treatment of attention deficit hyperactivity disorder, ADHD. Most of the questions, as will be articulated by the FDA, concern safety issues.

Yesterday there was a meeting of the Pediatric Advisory Committee which discussed a range of safety issues concerning medications used in the treatment of ADHD, the stimulants as well as Strattera, and actually some data emerged on modafinil as well during those discussions. I was present as an observer during those meetings. I am glad I was there. Some of the members of the committee that are here today were also present yesterday so I think a lot of heavy lifting was done yesterday on some of these important side

effect issues that will help inform us in our deliberations today.

My remarks are going to be unusually brief, in part because my voice is strained. My voice has not been cooperating for the last few days. In fact, sometimes I am not sure it is my voice--I don't know what kind of symptom that would mean. But we have a backup plan. Danny Pine, when he comes here, in case my voice fails, he will become my voice.

I also want to put you on notice that Cicely Reese may deliver at any moment! I am not kidding! So, we have plans for her transportation and replacement should that occur. Please bear with us under these circumstances.

Now I would just like to go around the table and ask everyone to introduce themselves. Let's start from the FDA end.

DR. LAUGHREN: Tom Laughren, from the Division of Psychiatry Products.

DR. ANDREASON: Paul Andreason, Division of Psychiatry Products.

DR. MANNHEIM: Glenn Mannheim, Division of Psychiatry Products.

DR. BIGBY: I am Michael Bigby, dermatologist from Boston.

DR. RAPPLEY: Marsha Rappley, Developmental Behavior Pediatrics, Michigan State University.

DR. WANG: Phil Wang, psychiatrist and epidemiologist from Harvard Medical School.

DR. REESE: Cicely Reese, executive secretary.

DR. GOODMAN: Wayne Goodman, chair of this committee as well as chair of the Department of Psychiatry, University of Florida.

DR. LEON: I am Andrew Leon, professor of biostatistics at Cornell Medical School.

DR. ROBINSON: I am Delbert Robinson. I am a psychiatrist at the Zucker Hillside Hospital and the Albert Einstein College of Medicine.

DR. PFEFFER: I am Cynthia Pfeffer, child and adolescent psychiatrist at Weill Medical College of Cornell University.

DR. ARMENTEROS: Jorge Armenteros, child and adolescent psychiatrist in Miami, Florida.

DR. WELLS: Barbara Wells, I am dean of the School of Pharmacy at the University of Mississippi.

MS. DOKKEN: I am Deborah Dokken. I am the patient family rep. on the Pediatric Advisory Committee.

DR. MALONE: I am Richard Malone, a child psychiatrist from Drexel University College of Medicine.

DR. MEHTA: Dilip Mehta, retired physician from the drug industry. I am the industry representative on the committee.

DR. GOODMAN: Thank you all very much. I think Daniel Pine will be joining us shortly. I would now like to turn the microphone over to Cicely Reese to go over some housekeeping, particularly the conflict of interest statements.

Conflict of Interest Statement

DR. REESE: The following announcement addresses the issue of conflict of interest and is

made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee's participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions:

In accordance with 18 USC, Section 208(b)(30, Dr. Wayne Goodman has been granted a full waiver for his employer's related contract with a competitor, funded between $100,001 and $300,000 per year. His employer also has related contracts with another competitor, funded for less than $100,001 per year.

Dr. Andrew Leon has been granted a waiver under 21 USC, 355(n)(4) for his ownership of stock in a competitor. This stock is valued from $5,001 to $25,000.

A copy of the waiver statements may be obtained by submitting a written request to the

agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Dilip Mehta has been invited to participate as an industry representative, acting on behalf of regulated industry. Dr. Mehta's role on this committee is to represent industry interests in general and not any one particular company. Dr. Mehta is retired from Pfizer.

In the event that the discussions involve any other products or firms not already on the agenda for which the FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firms whose products they wish to comment upon. Thank you.

DR. GOODMAN: Dr. Daniel Pine just joined

us so I wonder if you could introduce yourself.

DR. PINE: Danny Pine, Chief of Developmental Studies, Mood and Anxiety Disorders Program, National Institute of Mental Health Intramural Research Program and I am a child and adolescent psychiatrist.

DR. GOODMAN: In a moment I will turn over the floor to Dr. Laughren who will give us the introductory remarks. I think for all of us who have read through these briefing materials one of the issues that emerges, that didn't surface during yesterday's discussions, are questions about dermatological reactions. I see that we will also have the benefit of an intensive review of those issues as well to help us in our decision-making today. So, Tom, would you please come forward? Thank you.

FDA Introductory Remarks

DR. LAUGHREN: I would like to welcome everyone to today's meeting. Before I introduce the topics for today's meeting I would like to acknowledge the service of one of your colleagues

on this committee whose term is ending in June, and that colleague is Wayne Goodman. This has been a particularly busy time for the committee, as you know, and Wayne has, of course, been the chair of the committee for much of this time. Serving on this committee, again as all of you know, is a very demanding and sometimes stressful task and I hope that you all understand how much we appreciate the help that you give us.

Now, Wayne told me after the September, 2004 meeting on antidepressants and suicidality in pediatric patients that he didn't have any friends anymore in the academic and clinical community. I just want to assure him that he always has friends here, at FDA.

[Laughter]

So, thank you, Wayne. This is a small token of our appreciation.

DR. GOODMAN: Thank you very much. I used to have a voice before I started this!

[Applause]

DR. LAUGHREN: Now, on to the topic for

today's meeting, we are going to focus on NDA 20-717, supplement 19. This is for modafinil in the treatment of attention deficit hyperactivity disorder. As you know, modafinil is marketed as Provigil to improve wakefulness in adults with excessive sleepiness associated with narcolepsy, obstructive sleep apnea syndrome and shift work sleep disorder. It is a Schedule IV drug and the recommended dose in these disorders in adults is 200 mg.

Now, Cephalon has provided us data in support of a claim for the safety and the short-term effectiveness of modafinil in the treatment of ADHD at a slightly higher dose, at a dose of 340 mg per day in children less than 30 kg and 425 mg per day in children greater than 30 kg. This supplement was submitted in December of 2004 and, as you know, we issued an approvable letter in October of last year.

Though we did issue an approvable letter, the letter addressed three concerns that we wanted to have further addressed. One of those was

serious skin rashes; a second was psychiatric adverse events; and, finally, there were three patients with transaminase elevations for which we wanted additional data.

The sponsor responded to our approvable letter, in November of last year, and today you will hear from several FDA staff. You will hear from the primary reviewer, Glenn Mannheim who, as you know having seen his review, has recommended against approving this drug based on his concerns about rash and several other adverse events.

You will also hear from Dr. Paul Andreason who will provide some additional comments on safety. Our presentations are going to focus entirely on the safety issues because we agree with the company on efficacy. But you will hear from the company on efficacy and, as well, you also have our reviews.

In addition, we have obtained advice on the dermatologic problems from our own internal consultants from Dermatology. You have their reviews, and Dr. Markham Luke, from the Dermatology

Division, is here to address any questions you might have. In addition, we have Dr. Michael Bigby, who is the chair of the Dermatology Advisory Committee, who will be making a presentation on serious drug-related rashes and he will be participating in the discussion as well.

Now, I want to be clear that the Division of Psychiatry Products has not reached a conclusion yet about this application. We have these concerns and that is precisely why we are coming to you to ask for your advice. After you have heard the findings and the arguments we are going to ask you to vote on two questions. The first question is focusing on efficacy questions, whether or not you believe that the company has demonstrated that this product is effective in the treatment of ADHD. Secondly, we will ask you to vote on the question of whether or not it has been shown to be acceptably safe in the treatment of this disorder.

In addition, we are going to be asking for your comments on several other issues related mostly to rash. First of all, if the drug were to

be approved for this indication we would like your advice on a risk management plan. We would like your advice on labeling, particularly for rash. Finally, we would like your advice on any postmarketing studies that you think might be useful to further clarify this problem. I think I will stop there and Dr. Mannheim will be presenting his findings. Thank you.

FDA Presentation

FDA Clinical Review

[Slide]

DR. MANNHEIM: As Dr. Laughren explained, I reviewed the initial submission for modafinil for this indication. I will review with you today the information specific to safety.

[Slide]

Here is an outline of what I will be covering. I will be reviewing a little bit of the background and history of modafinil; an overview of the safety database; common adverse events in Cephalon's clinical trial; other adverse events of significance; psychiatric adverse events; and, most

importantly, rashes and what I think the potential public health impact may be. Then I will give you some closing comments, and I will be followed by Dr. Andreason.

[Slide]

In 1998 modafinil was approved as a wakefulness-promoting agent in adults with excessive daytime sleepiness associated with narcolepsy. Additional indications were granted by FDA in 2003 for excessive daytime sleepiness associated with obstructive sleep apnea/hypopnea syndrome and shift work sleep disorder.

The important thing that I would like you to notice from this slide is the dose. The recommended dosing was 200 mg once a day which, based on a 65 kg adult, comes to about 2.67 or 2.7 mg/kg. I want you to remember those numbers since we will come to it in other slides. Recommendations were to give modafinil, Provigil, as a single morning dose for narcolepsy or obstructive sleep apnea or for shift work sleep disorder one hour prior to the start of the work

shift. No additional benefit was shown for doses more than 200 mg.

[Slide]

The current application is for use of modafinil in children and adolescents with ADHD. Two doses have been proposed by Cephalon. For children less than 65 lbs or 30 kg, they would be getting a single daily dose of 340 mg. For children or adolescents more than 65 lbs or 30 kg, they would be getting a dose of 425 mg a day.

Now, remember the number 2.6. For the highest dose in children, on a milligram/kilogram basis, the children would be getting 21 mg/kg or about 8 times higher than the adult dose. For those over 65 lbs or 30 kg the highest dose would be 5.3 times higher than the adult dose. Cephalon is recommending that children or adolescents start the drug at initial doses of 85 mg and slowly titrate up, based on tolerability, by incremental steps of 85 mg to the targeted dose of 340 mg or 425 mg a day.

[Slide]

This shows the population which was studied in the submission. It was children and adolescents 6-17 years of age with DSM-IV ADHD who attended a full-time school. These were moderately to severely ill children. They had minimal learning difficulties. As it relates to adverse events, children with psychiatric comorbidities were excluded. Stimulant non-responders were not allowed in the trial. Those with abnormal laboratory or medical conditions one month prior to the start of the study were also excluded.

[Slide]

There are three studies which are called the pivotal studies for this. Study 309 and 311 were 2 9-week, double-blind, flexible dose, weekly titration studies. Study 310 was a 7-week, double-blind, fixed dose study, followed by a 2-week randomized withdrawal to modafinil or placebo. Children less than 65 lbs went on 340 mg a day and those over 65 lbs went on 425 mg a day.

[Slide]

This slide shows the total number of

subjects and doses used in the Phase 3 double-blind, placebo-controlled trial. Of note, 420 subjects were treated with modafinil and 213 subjects were treated with placebo. The important thing to note here is the numbers 102, 256 or 358. Children and adolescents only received the proposed labeled efficacious doses.

[Slide]

This slide comes from Cephalon's briefing document which was submitted for your consideration by Cephalon. It summarizes the pediatric trials. The 420 comes from the Phase 3 double-blind exposure. The number I want to show here is the number 933 because this constitutes the core safety database of this supplemental NDA. This slide indicates that additional 303 children were exposed to modafinil in an open-label ongoing Phase 3 trial. About 400 other children for obstructive sleep apnea and narcolepsy are the legacy studies.

As far as the purposes of this submission, we are only considering the number 933 since we don't have an integrated safety database for the

other 689 children and they were not part of this submission. It certainly would be reassuring if there were no adverse events in these subjects but we really don't know at this point.

[Slide]

This slide is a little busy and I apologize for that. It shows exposure to modafinil and modafinil metabolites and compares it with what one sees in clinically used doses in adults with those proposed for children. What I want to bring your attention to is the exposure of the modafinil sulfone as measured by the total exposure area under the curve. In adults, with an initial dose of 200 mg, the average area under the curve is 38 or close to 40. Going to the highest child, receiving 425 mg, the area under the curve of the sulfone is about 250. This is 6.5 times higher than the exposure seen in adults. Going to the lowest dose of children receiving 340 mg, the average area under the curve is around 630. This is 16 times higher than that seen in adults with clinical dosing. This cannot be explained by

differences in dosing on a milligram/kilogram basis. These are clinically used doses and with them one sees that the sulfone metabolite is much higher compared to adults.

[Slide]

Now we are going to look at the adverse event data.

[Slide]

The incidence of common treatment-emergent adverse events in the Phase 3 double-blind, placebo-controlled trial is listed. Of note, insomnia occurred in 27 percent of subjects on modafinil and 4 percent of subjects on placebo. Anorexia occurred in 16 percent of subjects on modafinil and 3 percent of subjects on placebo. Perhaps associated with that, there was weight loss in 4 percent of subjects on modafinil and 1 percent of subjects on placebo.

[Slide]

Notable psychiatric adverse events include psychosis in 0.5 percent, as listed here, and suicidal events in 6 subjects, 0.6 percent. The

suicidal events included 5 ideations; 1 attempt. None were completed. Yesterday Dr. Mosholder reported on a pooled analysis of the ADHD trials and that suicidal behavior was infrequent among the non-medicated ADHD placebo subjects.

[Slide]

Other clinically significant adverse events which were noted in this trial consisted of gastric or duodenal ulcers in 2 subjects. One case of note was a child who was admitted to the hospital with a moderate metabolic acidosis who had an H. pylori infection.

There were 9 cases of syncope in the total exposure. Of note is a child who, according to the vignette information, had a 40-minute bradycardia, hypotensive syncopal episode and one week later an EKG was performed which showed AV dissociation with adjunctional rhythm. There were 24 children who were quoted as having asthma.

Of note is a subject in one of the pivotal trials, 310, who, 8 days after being started on modafinil at a dose of 340 mg collapsed at school

during gym, stopped breathing momentarily and was given an inhaler and began breathing normally. This was diagnosed as an acute asthma attack and the child was discontinued from the study on day 9.

There were 3 subjects who had dehydration, and of note is a subject in the open-label continuation trial who, on day 147 of treatment, was admitted to hospital with severe dehydration, moderate ketoacidosis and hypoglycemia which was found secondary to a strep. throat.

Sixteen subjects had laboratory evidence of hepatocellular injury based on transaminases being greater than 3 times the upper limit of normal. Of note, there were no cases of jaundice or liver failure, or no significant bilirubin elevations.

[Slide]

Now I am going to talk to you about the rashes but I am not a dermatologist and I am relying on FDA's dermatologist, Dr. Porres who did a consult, and someone from FDA from Dermatology is here to answer some questions.

When you look at all the subjects who were exposed, rashes were present in 5 percent of all subjects compared to 4 percent that you saw in the Phase 3 double-blind, placebo-controlled trial versus 2 percent in placebo. Only 1 subject dropped out in the double-blind, placebo-controlled Phase 3 trial, which was an 8-week, study, because of a rash.

When you look at all the studies, including the open-label safety study, 101 subjects dropped out because of an adverse event, of which 26 percent were noted to have a rash in their vignettes although it may not have been coded as a reason for discontinuation. In one-half of these subjects, or 13 subjects, the rash was coded as a primary reason for discontinuation. The rashes varied in spectrum of severity. Eight with rash also had fever; 2 with rash had elevated liver function tests, one with a transaminase of 17 times the upper limit of normal.

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I am now going to discuss some of the

serious skin rashes, primarily the erythema multiforme, Stevens-Johnson which, from my standing as a pediatric neurologist are usually hypersensitivity reactions to drugs. There were 2 rashes which were thought to be erythema multiforme, Stevens-Johnson.

One subject had peeling and blistering over the entire body, with lips and urinary tract involvement, in study 311. The drug was stopped but the rash progressed to involve peeling, blistering, mucosal involvement over days. In another subject in study 207 the drug was stopped but the rash progressed. The child was hospitalized.

Other rashes of note included a child in study 207 with vesiculobullous cheeks with severe lip blisters. In study 312 another subject had a rash where there is no clear description but the rash was obviously severe enough that he was treated with systemic steroids, prednisone and given Benadryl. The rash recurred when restarted at 85 mg on day 34. There are two cases of

positive, you know, rechallenge.

[Slide]

Other skin reactions of note--there were possible allergic events in about 22 of the subjects out of the total exposure of 933 subjects, at 2.4 percent. They included hives, urticaria; facial edema; pruritus; allergic reactions; red lips; eczema with increased LFTs. There were some non-allergic events of alopecia, tongue blotches, Herpes zoster, plantar warts and ringworm.

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Now I would like to give some more details about the index cases here. Case number one was a young girl with an unremarkable medical history who had attention deficit disorder. She was started and then titrated over 2 weeks to a target dose of either 340 mg or 425 mg a day, but it differs in 2 different vignettes. Two days later, on day 16, the child developed a fever of almost 102, sore throat, mild rash which was described as red bumps. The next day the child was seen in the emergency room. My understanding is they thought the child

had strep. throat and they gave one dose of amoxicillin which was subsequently stopped. The next day, day 18, the modafinil was stopped. Over the next 4 days the rash worsened and progressed. There were multiple pruritic areas over the arms and stomach. On day 22 the rash progressed to involve the face. On day 23 mucosal involvement was said to be present in 2 areas. It burned when the child urinated so there was involvement of the urethra. The child had swollen and crusty lips. At some time later--the exact course is uncertain from the vignettes--there was extensive skin peeling involving the palms and soles. No new lesions were said to be present by day 30 and the event was said to be resolved. By day 31 or day 26--it differs in 2 vignettes--the child was given 1 more dose of modafinil by the mother for unclear reasons and the itching returned. On day 44 the child was withdrawn from the study and the vignette indicates the Stevens-Johnson syndrome resolved but the erythema multiforme continued.

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This case involves a young child with inattentive deficit disorder who also had Turner's syndrome and bed-wetting, who was on somatotropin for the Turner syndrome for 7.5 years prior and desmopressin for the bed-wetting for 4 months prior. She was started, titrated on modafinil 200 mg a day for week 1 of the study and then 100 mg a day for week 2 of the study. By day 4 she developed fever, abdominal pain and diarrhea. This lasted for 9 days. By day 14 the child was seen in the emergency room for pruritic urticaria involving the face and chest. The drug was stopped. The child was treated with diphenhydramine. The rash worsened by day 15. The child was then hospitalized with a provisional diagnosis of Stevens-Johnson. The child was seen by a dermatologist who found no evidence of mucosal involvement but was diagnosed as a moderate morbilliform rash. The child was treated with hydroxyzine. This rash resolved in 1 week. This case was accepted by Cephalon as being compatible with Stevens-Johnson syndrome.

[Slide]

Another subject of note is a young boy who was started on modafinil at 400 mg a day for 2.5 weeks, and on day 14 developed fever and a moderate rash on the cheeks. The rash progressed. By day 17 there was severe blistering on the lips. The rash was described as vesiculobullous. On day 19 the modafinil was stopped. The time course of everything else was not specified in the vignette and no more information is available. The child was treated with cephalexin for the rash and Tylenol with codeine for fever and pain.

[Slide]

Dr. Porres, of the Division of Dermatology at FDA, reviewed the 21 cases identified in my initial review and the entire safety database of this submission. He divided the cases into three categories, definite cases representing erythema multiforme, Stevens-Johnson. There are 2 subjects there or 0.2 percent; subjects who had a history consistent with early prodromal erythema multiforme and Stevens-Johnson, there were 3 subjects, 0.32

percent; and then there were 7 additional subjects who had a history suggestive of prodromal erythema multiforme, Stevens-Johnson. So, 10 more subjects plus the 2 subjects, or 12 subjects, so this is a total of 1.25 percent of subjects with definite and potential erythema multiforme, Stevens-Johnson.

[Slide]

When one looks at the postmarketing experience with modafinil, there were 6 reports of serious skin reactions. All occurred in adults 18 and over. There were 5 biopsy confirmed cases of erythema multiforme, Stevens-Johnson. Four were hospitalized and 1 died, but this case was really confounded by other medications and medical conditions. There was 1 dermatitis bullous. Because of the under-reporting, the true number of cases is probably likely to be greater. But the take-home message that I would like to say is that this slide shows that biopsy confirmed Stevens-Johnson syndrome occurred in adults at lower exposures than those received by children.

[Slide]

Erythema multiforme or Stevens-Johnson syndrome is generally thought to be hypersensitivity reactions to drugs.

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One of the cases which was really interesting involved a child who developed urticaria, facial edema, fever and a 17-fold elevation in transaminase between 10-14 days after starting the drug. The child had a history of allergy to sulfamethoxazole trimethoprim. Sulfamethoxazole is a sulfonamide and is one of the drugs known to cause Stevens-Johnson. It is structurally similar to modafinil sulfone, which raises the question of a possible cross-sensitivity to the sulfone metabolite.

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What is the potential public health impact of these findings? Two recent estimates of the background rate for erythema multiforme, Stevens-Johnson was 1-2/million/ year. In this submission there were 2 subjects with erythema multiforme and 10 other possible cases of a

significant rash. The total range of risk is anywhere between 0.2 percent to 1.3 percent.

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A recent CDC study estimated that 2.5 million children, ages 4-17, were on ADHD medication. Now, if we assume that only 10 percent of these children will try modafinil at some point, then we ask the next question, how many cases would result.

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We estimated that there would be a range between 500 and 3,000 cases which will occur based on the 0.2 percent to the 1.3 percent incidence among the 10 percent who are switched to modafinil. Based on the known mortality associated with erythema multiforme, Stevens-Johnson, we would expect from 15 to over 400 deaths to occur. We conclude that even though a crude estimate can only be made at this time, a potential exists for a significant number of cases to occur post-approval since ADHD is so prevalent.

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The question is can one label for this? Can we prevent this? Dr. Le Grenade and her co-authors at FDA recently published a paper on Stevens-Johnson syndrome and toxic epidermal necrolysis in association with selective COX-2 inhibitors. I quote from her and I italicized certain areas: There is no satisfactory method for determining who is at greatest risk for developing drug-associated Stevens-Johnson syndrome and toxic epidermal necrolysis and hence of preventing it, short of avoiding drugs altogether. There has been a single study suggesting that early withdrawal of the agent at the first sign of illness may improve the outcome. Although this intuitively makes sense, this study needs to be replicated. Even if it is proven correct, its practical application will be limited because it is very difficult to identify the very earliest lesion in a timely manner because of the rapidly progressive nature of this illness and the non-specific features of its prodrome.

In the cases observed with modafinil in

this submission in children no deaths occurred. The rash progressed after the drug was stopped and the children recovered. It may not be so next time.

[Slide]

ADHD is a serious condition--I will give you closing comments--it is a serious condition which is usually not considered to be associated with a fatal outcome. Exposure to a sulfone metabolite is significantly greater, up to 16 times more in children than in adults. This raises questions about the relevancy of the adult safety experiences to pediatric use.

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The relationship of this metabolite to rash is purely speculative but it has structural similarities to drugs known to cause erythema multiforme and Stevens-Johnson syndrome which can be fatal.

The incidence of erythema multiforme, Stevens-Johnson syndrome observed in these studies is, at a minimum, hundreds of times the background.

The age ranges of the rashes appear skewed towards subjects less than 12 years, those having a higher sulfone exposure. Doses lower than 340 mg have been shown to limit efficacy, hence, dose reduction is not a reliable option.

[Slide]

Although some cases with rash got better, there were 2 positive rechallenges and one case progressed after discontinuing the drug. One subject with rash was hospitalized but there was disagreement about the diagnosis. One child with a history of reactions to sulfa drugs developed a hypersensitivity reaction with transaminase elevation 17 times the upper limit of normal, with urticaria, fever and facial edema 10 days after starting modafinil, which raises the hypothesis of cross-sensitivity with sulfa drugs.

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Psychosis and suicidality, although not standardly significant, were more frequent in subjects on modafinil than with placebo. Insomnia was present in 27 percent of subjects on modafinil

versus 4 percent in placebo, and anorexia occurred in 16 percent of subjects on modafinil versus 3 percent on placebo in the double-blind, Phase 3 trials.

[Slide]

This review was very much a team effort of my many colleagues at FDA, some of whom I am blessed to call my friends. Thank you.

DR. GOODMAN: Before you step down, could you review any cardiovascular effects, effects on heart rate and blood pressure?

DR. MANNHEIM: Dr. Andreason is going to do that.

Modafinil for the Treatment of ADHD

DR. ANDREASON: Good morning.

[Slide]

My name is Paul Andreason and I am the Acting Deputy Director of the Division of Psychiatry Products. I would like to talk to you this morning about modafinil in the treatment of ADHD.

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Dr. Mannheim has outlined the concerns that he has about modafinil in the treatment of ADHD, and I think what we are faced with as we look especially at the skin rashes is what I like to call incongruity of data. I will get into that in a little bit. I would also like to acknowledge the Neurology Products Division where the drug resides--it is kind of its home since it was approved there first--and the safety team for helping us out with the background rates for Stevens-Johnson and looking at the adverse event reports through the Adverse Event Reporting System and their epidemiologic expertise.

Glenn did the primary review on the first submission. June Cai helped out with the review of the response to the approval letter. In the Division of Dermatology, I would like to thank Joe Porres and Markham Luke, who is here with us today--Markham is here with us today. Joe took another job and he is not with the Division of Dermatology right now. Then, in the Division of Drug Risk Evaluation, I would like to thank Andy

Mosholder and Kate Gelperin who, as part of their presentation yesterday, did an analysis of the psychiatric adverse events that are associated with modafinil use.

[Slide]

Just as a quick review of how we workup safety problems with drugs or safety profiles of drugs, I should say, when we look at a drug we look at deaths, serious adverse events, adverse dropouts, potentially clinically significant labs, ECG and vital signs and then we develop information on comparative common and drug-related adverse events, all these things from controlled trials. We also do special searches, especially in this case with modafinil and many psychiatric drugs--well, all psychiatric drugs, for psychiatric adverse events; in this case, for Stevens-Johnson syndrome and neutropenia because these were things that kind of popped up; and then the recent interest in blood pressure, pulse and cardiovascular adverse events. Then with the response to the approvable letter we get a safety

update. In that safety update we focus on serious adverse events and deaths, if they occur. We develop our profile of the common and drug-related adverse events from the controlled trial data, as well as the comparative information on labs, ECGs and vital signs.

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Modafinil is a marketed product and we got some information from Verispan about the exposure to modafinil at this point. These are numbers not in patient-years but in unique patients. At all ages at this point between the years 2002 to 2005 there were 1,087,000, roughly 1,088,000 exposures in all ages, and for children ages 0-17 there were roughly 36,000 exposures.

I kind of want you to keep that in mind because this is the first piece of what I would call inconsistent data about rash. It is almost unheard of to see cases of Stevens-Johnson syndrome in controlled trial data and here we have at least nominally 2 cases that have been identified as such. At that kind of a rate you would expect to

see something in the adverse event reporting data. Dr. Mannheim said, well, based on these numbers, these would be the projected number of cases that we would see after marketing. The piece of incongruity here is that the drug is already marketed. We have 36,000 exposures in the age ranges that were studied, and in the 0-12 group right around 11,000 and we have no AERS-reported cases.

Now, one of the cases from the controlled trial data actually is a duplicate case. It got reported in AERS but there are no spontaneous reported cases. So, given that kind of projection, I would expect to see some cases reported in AERS and we haven't seen that yet.

[Slide]

This is, again, a review of patient exposure in the controlled trial database. In the safety update we did get some information on serious adverse events and dropouts, as well as deaths, and Stevens-Johnson syndrome would be considered in that group. So, as more and more

information comes in, you know, that denominator of cases reported per amount of exposure changes, however, even with 2 cases in 1,600 that would still be a large number.

[Slide]

I think the problem that comes about when we look at Stevens-Johnson--and we will hear more from Dr. Bigby in a moment about how that ascertainment is made--is that in these two cases one was hospitalized and one was not. Neither of them were in a burn unit or the ICU and we don't have biopsy information on those kids.

[Slide]

These are tables that you have already seen. It reviews the numbers of patients exposed in the three pivotal trials.

[Slide]

Now, this is a table that shows you the common adverse event profile. Our usual definition of common and drug-related is adverse events that occur at least 5 percent of the time and occur at a rate that is twice placebo. In italics you will

see that anorexia and insomnia meet that criteria. There are a couple of other adverse events that are close but don't quite make that cutoff. This is the table actually that is proposed in labeling and is the usual kind of table that we have in labeling.

[Slide]

Just as a quick overview of the safety results from the controlled trials, there were no deaths and, of the adverse events of note, there were these 2 cases that were identified as either Stevens-Johnson or erythema multiforme. There were no new cases of leukopenia in the AERS system update, and we could see no real signal for leukopenia in the controlled trial data.

As far as psychiatric events, there were 4 suicide-related adverse events, no completed suicides. I will talk more about those in a moment. There were none in the placebo group.

As far as mean blood pressure changes, modafinil actually showed a slight decrease compared to placebo in mean blood pressure.

However, the numbers of patients that met the outlier criteria of systolic blood pressure of greater than 130 and an increase in greater than 20 mmHg were 9/420 for modafinil and 1/213. With pulse there was no difference in the mean value either, and the numbers for outliers are 6/420 versus 2/213. The 6 versus 2 in those 2 groups is, in my opinion, not terribly different. There was some weight loss, 0.7 kg weight loss with modafinil versus 1.0 kg mean weight gain in the placebo group.

So, did that answer your question about blood pressure?

DR. GOODMAN: Yes.

DR. ANDREASON: Great!

[Slide]

As far as psychiatric adverse events, this is drawn from one of Andy Mosholder's slides from yesterday. These were the comparative numbers with patient-year exposure, and these are real years. They are not multiplied. So, with 33 patient-years exposure in placebo you have no cases of mania or

psychosis or suicide-related adverse events. But there were 5 cases of aggression, spontaneously reported aggression. Zero cells are kind of tough to deal with when you are doing statistical analysis, but oftentimes you can use a Fisher's exact test to get at least some idea of whether or not something is statistically significant. I will show you that for the suicide-related adverse events on the next slide.

You will notice that numerically the cases of aggression are slightly less with modafinil than they are with placebo. As Dr. Mosholder stated yesterday, that was not a significant difference but it is not, by the same token, greater. In the open-label data it shows that the rates are lower. That doesn't necessarily mean--well, let me put it this way, these are patients, once they reach open-label, who have tolerated the drug and I think that probably the best comparison for this is the controlled trial data.

[Slide]

These are the results of the Fisher's

exact test for suicide-related adverse events. You see here that you have the 4 cases in the modafinil and that is compared to no suicide-related adverse events in the 660 in placebo. So, that ends up with a 2-tail value of p of 0.31 and 1-tailed p of 0.22.

[Slide]

Just to give you kind of a comparison with, say, Strattera that has received labeling for suicide-related adverse events, with Strattera there were 6/1357 versus 0/851. Because of the increased sample size, those numbers ended up being statistically significant. There were 5 cases of ideation and 1 attempt in the FDA defined cases. I would like to note that Eli Lilly has slightly different numbers because they had a slightly different definition of the suicide-related adverse events. They had 7 versus 1 out of 1357 and 851 respectively. That p value ended up being 0.07. Traditionally, for safety-related topics we don't necessarily use a p of 0.05 like we do for efficacy. We use a p of 0.1. So, using a cutoff

of a p of 0.1, the 0.7 would still be statistically significant. And, Strattera has a boxed warning.

Now, with the modafinil there are 4/664 versus 0/308. This is not statistically significant by Fisher's exact and all were cases of ideation and 3 of the cases actually resolved without discontinuation of the drug. The sponsor proposes warning language in labeling as opposed to boxed language.

[Slide]

As far as the cases of severe rash that are identified as Stevens-Johnson syndrome, we will hear more about that, again, from Dr. Bigby, and Dr. Markham Luke is here today to talk about the cases individually if people have questions on those.

The problem that we have with almost any adverse event report ascertainment, there was no histopathology with either of these cases. With Stevens-Johnson syndrome admission to burn units and ICUs is common. One of the kids was hospitalized but not in an ICU or burn unit. The

other child was treated as an outpatient. You have heard about the cases. I can go back to those if anyone has any questions. Again, there were no children in the postmarketing Adverse Event Reporting System, other than the one case that is the duplicate from the controlled trial.

There were 4 adults in the AERS postmarketing database, and it turned out that 3 had confirmatory histopathology and the other one was erythema multiforme without histopathology. There were no adults with Stevens-Johnson identified in the adult controlled trial database.

[Slide]

So, what we are left with from this controlled trial database, along with the open-label material that goes with it, is 2 serious cases, one admitted to the hospital, neither to the ICU or burn unit; none in the placebo group; 10 dropouts due to rash versus no dropouts due to rash in the placebo group. Spontaneous adverse events in the controlled trial, about 4 percent for modafinil versus 1 percent for rash, for all kinds

of rash.

But then, the incongruity here is that there are no other children with either Stevens-Johnson syndrome in the postmarketing adverse event database with about 36,000 kids exposed. Again, with that kind of exposure and the projected numbers of cases of SJS, based on 2/933 or even 2/1,600, one would expect to see more in the Adverse Event Reporting System.

[Slide]

So, just to compare and contrast labeling with Lamictal that carries a boxed warning for Stevens-Johnson syndrome, in that boxed warning there are some fairly hard numbers. For example, they did a prospective registry study and there was one death due to Stevens-Johnson syndrome with Lamictal out of 1983 patients. There was also information on rates in adults with different kinds of diagnoses, for example, 8/1000 in children with Lennox Gasteau and 3/1000 adults. Then in the bipolar population it was 1.3/1000 adults on adjunctive therapy for bipolar disorder. So, those

are some fairly hard numbers.

On the modafinil side, the sponsor proposes warning language and I have listed under here the points to compare and contrast with Lamictal. There are no deaths reported. Actually, on one of the slides that Dr. Mannheim presented, he said there was one death. That case was a fellow who came in to the hospital and had a subarachnoid hemorrhage and was treated with several drugs, one of which was phenytoin, known to be associated with Stevens-Johnson syndrome. He developed Stevens-Johnson syndrome as part of the course of his hospitalization and apparently was treated with modafinil prior to that hospitalization. So, I think that case is terribly confounded and I wouldn't count that as drug related, or I don't think we could count that one as a good drug-related case. So, based on my exclusion of that case, there would be no deaths so far due to Stevens-Johnson.

The child cases were not severe enough to require burn unit or ICU. Now, again back to this,

there are at least 2 nominally identified cases out of the 933 in the submission that were identified but there is no biopsy confirmation. Back to the other part of the incongruity, there are 36,000 exposures already with no cases. Then back to the other side, you have 3 confirmed cases of adult SJS in the postmarketing but that is with 1.5 million. So, that is getting close to the background. Depending on how you factor in under-reporting, you know, there could be association and increased risk for Stevens-Johnson.

[Slide]

So, I guess in the end the question that you need to think about is if there is an increased risk of Stevens-Johnson syndrome associated with modafinil, what would be an acceptable risk. And, if modafinil were considered for approval, what kind of risk management program would you want to implement, and how should the concern about serious skin rashes be addressed in product labeling. Again, you have the examples of labeling and I can go over those a little more if you would like.

And, should there be a requirement for postmarketing studies, if approved, to better understand the skin rashes?

There was one slide, as a bit of a digression that Dr. Mannheim showed about liver enzymes, he included GGT in a slide, along with ALT and AST as a percentage of increased liver enzymes under the heading of hepatocellular injury. Usually we look at ALT, AST and bilirubin as signs of hepatocellular injury and don't necessarily include GGT. Excluding GGT, there were 3/420 cases of elevation of ALT and AST of greater than 3 times the upper limit of normal, for a percentage of 0.7. In placebo there was 1/213, for a percentage of 0.5, and I don't see that as meaningfully different.

So, that concludes my remarks about modafinil and I would be happy to entertain any questions.

DR. GOODMAN: Thank you. I understand there is going to be a change of technology before the next presentation. Is that correct? Yes? So,

why don't we start doing that but I wonder if you can stay for questions that this committee may have. Let me start that off.

Of the 35,000 or so children who have been exposed to modafinil postmarketing, how many of them were on the doses that are proposed to be used in ADHD? I would suppose further that that would be mostly for Mexico where it is already approved.

DR. ANDREASON: I am not sure. By the way, those numbers are for the United States only.

DR. GOODMAN: So, if they are for the United States only let me go back and rephrase it. How many of them would be in the dose range that is proposed for ADHD?

DR. ANDREASON: Yes, we tried to track that down and found that it was impossible to get that kind of information. I think the only thing you could do would be to assume that they had received the maximum recommended dose, which was only 200.

DR. GOODMAN: We have one of our committee members that I would like to see introduce herself,

Jean Bronstein.

MS. BRONSTEIN: Good morning. I am Jean Bronstein. I am a nurse and consumer representative for the committee, and I apologize for being a little late. But I do have a question. I am trying to understand some 300 patients, I believe, that have dropped out of the study, and I am wondering if the rash numbers are also representative of all patients having dropped out of the study at some point. Is that clear?

DR. ANDREASON: The patients who dropped out due to rash are included in those numbers, yes.

MS. BRONSTEIN: They are? Thank you.

DR. GOODMAN: Any other questions around the table or are we ready to proceed with the presentation?

DR. WANG: It is actually a follow-up to Wayne's question. In the negotiations for these pivotal trials how were the doses chosen? Why was, you know, 300 mg, 400 mg chosen? For the wakefulness indication it is 200 with no additional benefit.

DR. LAUGHREN: Paul, you may be able to say more about this, but my understanding is that there was a Phase 2 study, a fixed dose study that looked at different doses, I think running from 100-400, that basically showed effects only at the higher doses and that was the basis for focusing on the higher doses in the pivotal trials.

DR. ANDREASON: I am sorry, I thought you were looking at Cephalon when you asked that question. But, yes, that is correct. Two of the studies were flexible dose studies in the pivotal trials and one of them was a fixed dose study.

DR. WANG: There is no data in here to suggest something that you have raised, Dr. Mannheim, that there is no potential benefit to trying lower doses. They don't look to be, you know, sort of clinically efficacious, which these data don't suggest.

DR. MANNHEIM: My understanding from the earlier Phase 2 trials was that lower doses didn't work and they had to get to these doses in order to show efficacy in ADHD. Cephalon can respond to

that.

DR. GOODMAN: Yes, maybe we can hear more about that from the sponsor during their presentation. We have Dr. Leon and then Dr. Mehta.

DR. LEON: I would like to follow-up on the number of exposed. Is that based strictly on the 7- or 9-week clinical trials out of which maybe about 40 percent dropped out? Or, does that include the follow-up as well? Is there slide on person-week exposure?

DR. ANDREASON: Oh, as far as the number of patients that are exposed for an adequate amount of time to count, I think what we came up with was as an estimate that was around 600. Again, if you say 2 cases out of 600, that makes the rate of it seem even higher. Then, it even makes it seem more implausible that we don't see anything in postmarketing. So, I think you are right, if Stevens-Johnson is something that shows up in the first 2-8 weeks of treatment the numbers in the controlled trials would be right around 600. The 900 includes patients that dropped out. It

includes patients that were in Phase 2 studies--excuse me, I take that back. The 933 includes patients that were in the open-label trials, so patients that were exposed for much longer.

When we looked at postmarketing data and estimates of exposure we didn't look at patient-year exposure because we wanted to focus on the fact that Stevens-Johnson we probably likely to show up in the first 2-8 weeks and if we looked at patient-year exposure the rate of background would start to drop with extended exposure if you looked at patient years instead of unique patients. That is why we chose to look at it that way.

DR. GOODMAN: Dr. Mehta?

DR. MEHTA: Is the dose of the drug relevant to the occurrence of Stevens-Johnson syndrome? I would have thought that this is a sensitivity reaction so it doesn't matter what came out of the drug that is used, that is, the dosage is irrelevant for the occurrence of SJS.

DR. ANDREASON: You will see from the

presentation coming up from the company that it didn't appear that the sulfone metabolite was increased any higher, than in other patients that didn't have rash, in the 2 patients that were identified as having rash. The expert is here to talk about that.

DR. BIGBY: Can I just make a quick comment about that?

DR. GOODMAN: Go ahead.

DR. BIGBY: It shouldn't make any difference in terms of the incidence of the rash. I think you are correct in that regard. The only way that I think it could affect the disorder is in outcome in terms of at a higher dose it will take a little bit longer to be cleared from the body so that the prognosis might be worse if you start with a higher dose because it may take longer to be eliminated.

DR. GOODMAN: Dr. Malone?

DR. MALONE: I just had a question about dosing. The stimulants are also used for daytime sleepiness disorders. Is the dose used for ADHD a

lot different than the dose used for daytime sleepiness?

DR. ANDREASON: Yes, it is higher. Daytime sleepiness and obstructive sleep apnea doses are 200. Right, Glenn? Then, for ADHD it is 300 and 425.

DR. RAPPLEY: No, I think he is asking about comparing the other stimulants? So, are the doses for Adderall or Ritalin higher for ADHD than they are--

DR. ANDREASON: I am sorry, I don't have that right at the top of my head.

DR. GOODMAN: Dr. Pfeffer?

DR. PFEFFER: I have a question about the pharmacokinetics of this drug, with the dose being so much higher in children, especially younger children, how is the drug metabolized? Also, is there a way of understanding if there are children who are slower metabolizers of this drug and, therefore, this is higher? Can we understand that? Is there a way of understanding also if there are certain children that might be assessed in terms of

the metabolism and understand that relative risk?

DR. ANDREASON: I can't really answer that question. I think we have somebody who can answer that question. Let me preface it by this though, I don't necessarily believe that ruling out the sulfone would be necessarily a guarantee of safety. In my opinion, I think the sulfone may be a bit of a red herring. I think with Lamictal we have no real idea why SJS occurs and it is much more common in kids than it is in adults. If they could come up with some kind of marker that would show what the risk was, that would be wonderful. I don't think in this case the sulfone reaches that kind of state. First of all, we have to identify whether or not there is a signal. Then, if one came to the conclusion that there was a signal, I still don't think that the sulfone would give us any assurance of safety regardless at this point.

DR. GOODMAN: Dr. Temple and then I want to go to Dr. Bigby's presentation.

DR. TEMPLE: I just wanted to observe that on the dose relatedness matter it is sort of

unusual to have almost an order of magnitude difference between what one group gets and what the other group gets. So, a lot of our experience with drugs will be looking at, you know, one- or two-fold differences and things like that. I am not sure one really could say that a marked difference in blood levels or exposure might not be related to rate. It could.

DR. ANDREASON: Ron Cavanaugh was the human biopharmacologist on this.

DR. GOODMAN: But then definitely Dr. Bigby.

DR. CAVANAUGH: Thank you. I agree with Dr. Andreason that at this point for the sulfone we really don't know any relationship for certain. It is purely at this point a plausible hypothesis. It is very structurally similar to the one drug which causes the highest incidence of Stevens-Johnson, blethamide, which is slightly different than many of the other sulfonamides in that it has a third oxygen in addition to the nitrogen and the sulfone. Modafinil also has that third oxygen in the same

position. We do not know. Basically, the only reason we looked at the sulfone was because of the dramatic higher amounts, as well as when Glenn asked me about the sulfone I immediately thought Stevens-Johnson and immediately thought sulfonamide. So, at this point we don't know.

In terms of the kinetics, from what I have seen, the metabolism does not seem to be particularly well defined. So, I really do not know at this point, you know, anything in terms of could specific metabolic pathways result in higher sulfone concentrations in some kids versus others. The concentrations that I see, and it is very poor, do not lead me to believe that the sulfone concentrations in these particular children--and there was only one child who had any measurement of the sulfone who had any of the Stevens-Johnson or other severe dermatologic reactions, and that sample was taken several days after the drug was discontinued. If I back calculate, it basically seems that for that one child the concentration was in the approximate range.

In terms of dose response, which was raised, we really have too few numbers here. You are also dealing with, you know, population numbers and you are dealing with 0.1 percent difference, 0.2 percent differences. There is no way you can be certain.

In terms of a dose related to hapten and degree of what is the likelihood of Stevens-Johnson or a hypersensitivity of any sort, I am not an immunologist; I do not know. One of the reasons we focused on AUC is because that gives you an idea of total exposure. When someone has already developed hypersensitivity and they have already had a history with a sulfonamide, they can get Stevens-Johnson with the very first dose of a drop, and there have been deaths in cases like that.

Really we are more talking about the development of hypersensitivity, and what you are developing as it being a hapten, my understanding is that it is the combination of, you know, developing hypersensitivity to the combination of the drug bound to certain proteins, or other things

in the body. So, with the higher exposure you are going to get more of this binding and, therefore, more antigenic exposure. The numbers are so small, we don't know. Also, with longer duration you would expect more stimulation.

I would really refer you to an immunologist. I really don't know, but the whole issue of dose response and everything else in terms of developing hypersensitivity, to me, is not clear.

DR. GOODMAN: Thank you. Thank you for being patient, Dr. Bigby. We are running behind schedule but the way I hope we may be able to make up some time is that I am going to cut lunch and I don't think we have that many public speakers. But I am determined to end at least at our scheduled time. During the sponsor presentations I would ask the committee members to restrict their questions to ones of clarification.

Serious Adverse Cutaneous Reactions to Drugs

DR. BIGBY: Good morning.

[Slide]

I am always impressed when I come down to sort of work in FDA committee meetings about the seriousness of what goes on here, and also the dedication that people have to trying to make rational decisions, and I hope my comments are helpful in your deliberations.

[Slide]

What I was going to talk about is serious adverse cutaneous reactions to drugs, and in order to do so I am going to cover three things. One is how to identify a drug eruption as a drug eruption and pin it down to a specific drug. We will look specifically at common eruptions, the serious eruptions, and I will end by showing you some things that are commonly mistaken for drug eruptions.

This is sort of a gold standard for determining that a rash is due to a drug. First you have to be sure that the rash you are looking at is a morphology that can be caused by drugs. You have to exclude alternative causes. You have to examine the relationship between the exposure to

the development of a rash in terms of the time interval; note the response to drug withdrawal, i.e., the rash will go away.

For many drugs there is information known about their proclivity to produce rashes, so what the frequency of rash is for a particular drugs. Then, in those rare cases where you actually do have a re-exposure, to determine what happens on re-exposure so you can be positive that it is a drug rash and looks like an eruption that is a classic eruption for drugs. You have excluded alternative causes; the interval from exposure to the development of a rash is correct in terms of what is known about that drug and that eruption. It goes away. Often I think the mistake people make about the response to withdrawal is that you expect it to go away very quickly when you withdraw the drug. For most eruptions that is not the case and the rash will actually take much, much longer than most people think to go away after you withdraw the drug. Then, oddly enough, re-exposure doesn't always produce the rash but when it does,

then you can be absolutely sure that you are looking at a definite cause. Where some of these things are missing, are judged to be probable or unlikely or not due to the drug at all.

[Slide]

Very quickly, we are going to look at these three common drug eruptions: exanthem which is the most common, urticaria and fixed-drug eruption. This is a patient with a widespread exanthematous drug eruption. It usually starts within the first 3 days after exposure to the drug. For some drugs like antibiotics and allopurinol that exposure window can be up to about 2 weeks. The rash is best described as small, erythematous papules that may coalesce. These patients have pruritus but they are not generally ill. Mucous membrane involvement is rare. It is a benign condition in that as the drug is withdrawn the patient gets better. They can often later in the course of the disease desquamate but they don't develop blisters and they don't have epidermal detachment.

[Slide]

There is very good data about this type of reaction. It has been studied in several prospectively collected data sets. One was the Boston Collaborative Drug Program. There is data on I think something like 35,000 exposures over about, you know, a 10-year period, collected in many hospitals.

[Slide]

You can say with fair certainty that there are certain drugs that have higher rates than others, and in this list the highest tends to be antibiotics. The highest rates are for amoxicillin and co-trimoxazole.

[Slide]

It is also helpful to know that there is a large list of drugs that are almost never associated with reactions. So, if a patient is on multiple drugs, which they often are, it is useful to refer to this type of list to exclude the ones that are least likely to be the culprit.

[Slide]

Urticaria you all know how to recognize. It is areas of swelling. There are usually plaque type lesions, and the key about urticaria is any individual lesion generally will last for less than 24 hours. Here is one of the perfect examples. If you identify the cause and you withdraw it patients will often have urticaria after such an exposure for weeks and even months even though you have identified the correct drug and withdrawn it.

[Slide]

The list of drugs that cause urticaria is very similar to the ones that produce exanthem.

[Slide]

Lastly, this is a fixed-drug eruption. A fixed-drug eruption is a really peculiar thing in that it tends to occur only on certain areas and to recur in those areas on re-exposure. It is the one instance where people will often be re-exposed because it is not so clear to the providers that this was, in fact, a drug eruption. The other reason that this is quite relevant is that the histopathology of a fixed-drug eruption is very

similar to what you see in erythema multiforme and, to a lesser degree, in Stevens-Johnson syndrome and toxic epidermal necrolysis.

[Slide]

Again, if you look at the drugs that cause fixed-drug eruptions, there is a lot of overlap between the drugs that most commonly cause all of these types of eruptions.

[Slide]

The three serious drug reactions that I want to talk about are the ones that I think are the most relevant to this question that you are asking today, and that is toxic epidermal necrolysis, Stevens-Johnson syndrome and the drug hypersensitivity syndrome.

[Slide]

Of all of the things which I have to say today, this is the slide that I want you to remember the most. These are two patients that I saw personally. These are people with toxic epidermal necrolysis. The most obvious and important thing about these patients is, number

one, that they are sick. They often have multiple mucous membranes involved. In severe cases not only are the sort of distal mucous membranes involved, but it can affect the trachea and even the bronchi.

The second most important thing is that they have widespread areas of cutaneous involvement and, in the case on the right, they often shed full-thickness necrotic skin over very large areas, and they have basically the equivalent of a widespread burn. The summary of toxic epidermal necrolysis in terms of its clinical features is also a prodrome of fever and malaise. This usually lasts one to two days. The eruption is predominantly on the face and torso. The lesions are best described as pruritic plaques. They can have bullae. Multiple mucosa are commonly involved. Patients with toxic epidermal necrolysis, however, do not have true target lesions. Probably by the best definition of toxic epidermal necrolysis, it has to involve at least 30 percent of the body surface area, and the mortality

for such described toxic epidermal necrolysis is quite high, around 30 percent. The majority of deaths are due to either infection or problems with respiratory distress that are either due to pneumonia or to the fact that the airway linings are involved.

[Slide]

As has already been mentioned, it is a relatively rare phenomenon so that in most population studies the incidence is about one case per million patient years; 95 percent of the cases clearly have a drug etiology, and there are certain drugs for which the incidence is much higher.

[Slide]

Based on a case-controlled study that was published in the New England Journal ten years ago, this was a study that carefully ascertained cases in France, Germany and Italy and to drug exposure histories from patients in three age and gender matched controls, and came up with an estimate of the number of cases per million exposures that one would see per week. It was highest for

sulfonamides. If you do the arithmetic, this turns out to be something in the order of 1 case in 200.00 or 250,000 for some of these drugs.

[Slide]

The drugs commonly associated with TEN are listed here. Again, these lists are very similar to the ones that cause benign eruptions and the same sort of drugs keep showing up: sulfonamides, hydantoins, some but not all of the nonsteroidals and allopurinol.

[Slide]

This is a patient with Stevens-Johnson syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis are dissimilar disorders in a continuum. The difference between Stevens-Johnson and TEN is one of degree of epidermal detachment. The symptoms are very similar. There is prodrome often of fever and malaise. The lesions are very similar. In Stevens-Johnson syndrome the area of involvement is usually defined as being less than 10 percent. It has a much lower mortality.

The other interesting thing is that if you

look at the etiology of Stevens-Johnson syndrome, it can be attributed to drugs in only about 50 percent of cases. Now, that seems to be in congress with TEN and SJS being part of a spectrum. I think the problem is that there is a lot of confusion about mixing up cases of erythema multiforme, which I think is a quite separable disease, with Stevens-Johnson syndrome. I think that explains why drug etiology is less commonly identified. I will have more to say about erythema multiforme at the very end.

[Slide]

Again, the incidence is about one per million per year, drug induced in about 50 percent. There is a higher incidence with some drugs and it is that same list of drugs, you should note.

[Slide]

Now, what I was saying about the relationship between SJS and TEN, TEN is defined as those cases where the area of involvement is more than 30 percent. SJS is less than 10 percent. Then, there are people who are kind of in the

middle, between 10-30 percent, that are called SJS/TEN overlap. The other thing to note is that erythema multiforme is not mentioned anywhere on this slide or in my previous comments because, as I said, I think it is a distinct disorder.

[Slide]

The last serious reaction that I wanted to talk to you about is the hypersensitivity syndrome. That is what this slide is an example of. It looks very similar to exanthem except for two things. When you have seen a few of these patients it always strikes you that the color in the hypersensitivity syndrome is a much brighter and darker red and the amount of confluence of the rash is much higher.

[Slide]

Symptomatically, these people have exanthem. They have fever, lymphadenopathy, often have hepatitis, some of them have arthritis. This is a disorder that has a significant mortality. It is not clear how patients should be treated and, again, the list of drugs that cause this that are

already known and sort of identified as such is very similar to the list of drugs that cause drug rashes in general.

[Slide]

This is a slide from a paper that was done by Roujeau and Stern, in the New England Journal, and it is a very busy slide. The only thing I want you to note is that the fatality rate for the hypersensitivity syndrome is about 10 percent. For TEN it is about 30 percent. For Stevens-Johnson syndrome, because of the area of involvement and severity it is much less; it is lower.

[Slide]

Finally, exposure to rash for TEN and SJS is in the order of weeks, so 1-3 weeks is noted in the third column in this slide. Skin biopsies are very helpful because in TEN and SJS they tend to show full-thickness epidermal necrosis, detachment of the skin at the dermal/epidermal junction, and often there is very, very little inflammation in the dermis associated with the rash.

[Slide]

Finally, I would like to conclude by showing you examples of things that are often called drug eruptions but are not, primarily erythema multiforme. Now, erythema multiforme--you can't make that diagnosis unless patients have typical target lesions. Typical target lesions have three rings, either a dusky or bullous center, an area of erythema around that and then a surrounding area of edemous skin. You can often actually have rings beyond that but if you have the three rings it is I think easily identifiable as erythema multiforme.

In terms of the distribution, another thing that is helpful is that erythema multiforme predominantly affects the face and the extremities. The torso is much less commonly and much less extensively involved. The majority of cases of erythema multiforme are actually associated with infection, herpes simplex being the most common one and, although it can be caused by drugs, drugs are a much, much less common etiologic factor for erythema multiform.

The other thing is that erythema multiforme, by and large, is a benign disorder. Patients recover and deaths are extremely rare for erythema multiforme. I think people shouldn't combine erythema multiforme, even erythema multiforme major with mucosal involvement with Stevens-Johnson because I think they are distinct entities.

Grover's disease is another one that looks to the world like a drug eruption. It tends to occur commonly in hospitalized males on their back and, you know, a lot of the times we get called for drug eruptions and it turns out to be just this scenario, elderly men with Grover's disease predominantly on their back.

Lastly, extensive cases of pityriasis rosea can be mistaken for drug eruptions. The key there is that, you know, the history is usually pretty classic. The distribution is classic as well and if you have the herald patches, as noted in the right-hand slide, there is not a lot of confusion.

The last two things on this list, the viral exanthem and graft versus host disease, no one can really distinguish those from drug exanthems or several other drug eruptions and it is a matter of great difficulty.

[Slide]

That is where I will stop. Thank you.

DR. GOODMAN: Thank you. Questions from the committee? Dr. Pine?

DR. PINE: I guess I am struggling a little bit, kind of like Dr. Andreason was. On the one hand, you know, the rashes were very concerning that were described. On the other hand, there are no cases in the spontaneous reporting. I was just wondering, given your background as somebody who sees this kind of thing every day presumably, or frequently, what was your impression when you reviewed the cases in terms of how convincing they were, number one and, number two, when you combine that with what you would expect to see how concerned, as a dermatologist who spends a lot of time thinking about this, were you about the data

that you saw and the cases that you saw?

DR. BIGBY: I think that the 7 year-old child that was described, to me, was a probable case of SJS that was drug related. After looking at the material, I think that the drug is going to be, and probably already is, associated with sort of an excess of cases of SJS/TEN.

DR. PINE: Thanks.

DR. GOODMAN: Dr. Rappley?

DR. RAPPLEY: I looked over 26 cases, I think it was, that had rash and I noted that many of those cases presented on a continuum that included fever, pharyngitis, rash, and it went from very mild to very severe. That is something in pediatrics that we see as a reaction with immunosuppression or reaction that, you know, reminds of Kawasaki's--not exactly but it makes me think of that. It reminds me of drug reactions. It reminds me of neutropenia. So, my question is do you see that as a continuum, those symptoms as related?

DR. BIGBY: I am actually not sure I

understand your question. I mean, of the material that I saw, I think that there was one case that probably had SJS. I think that the other sort of rashes described--

DR. RAPPLEY: So, you don't see that as a continuum?

DR. No--

DR. RAPPLEY: You see Stevens-Johnson as a very discrete--

DR. BIGBY: Yes, right. You know, I think that eruptions are sort of specific things to dermatologists and these things don't sort of fit together as a gestalt for a kind of reaction to that drug, no.

DR. RAPPLEY: Okay.

DR. GOODMAN: What I would like to do is take an unscheduled quick break, seven minutes. Before we do that, just an admonishment, I would like to remind the committee that, in the spirit of the Federal Advisory Committee Act and Sunshine Amendment, discussions about today's topic should take place in the forum of this meeting only and

not during lunch breaks or in private sessions. We ask that the press honor the obligations of the committee as well. If you will allow the committee members to exit the room first to take their break, we will reconvene in seven minutes. Thank you.

[Brief recess]

DR. GOODMAN: We are resuming now with a series of presentations from the sponsors. Please, committee members, restrict any burning questions to those of clarification. I think that we will go to lunch at 12:30 instead of 12:00, which means that we save time for more detailed questions of the sponsor after the public presentations. Please go ahead.

Sponsor Presentation

Introduction

DR. RACZKOWSKI: Good morning.

[Slide]

Dr. Goodman, members of the advisory committee, Dr. Laughren, FDA representatives, ladies and gentlemen, today we will be discussing the application for Sparlon tablets for approval

for treatment in pediatric patients with ADHD.

[Slide]

My name is Victor Raczkowski and I am the vice president for worldwide regulatory affairs at Cephalon.

[Slide]

Our proposed indication for Sparlon is for the treatment of ADHD in children as well as adolescent patients. We filed our application in December of 2004 and we received an approvable letter about ten months later. We submitted a complete response then to the agency in November of last year.

[Slide]

Sparlon contains the active ingredient modafinil which is also contained in Provigil tablets. So, modafinil is not a new chemical entity. Sparlon tablets have been formulated to facilitate administration to pediatric patients. That is, on a milligram/kilogram basis of modafinil they are smaller than Provigil tablets. They come in dosage that ranges in strength from 85-425 mg

and are intended for once daily administration in the morning.

[Slide]

Provigil has been marketed in the United States since 1999 and is currently marketed in 28 countries worldwide. Provigil is a wakefulness promoting product and it is approved in the United States in adults with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome or shift work sleep disorder. We have estimated exposure globally through the end of February 2006 as being approximately 780,000 patient-treatment years, of which 30,000 patient-treatment years are in pediatric patients. Modafinil is also listed in Schedule IV of the Controlled Substances Act.

[Slide]

You have been asked to address a number of questions today and the two voting questions are on the efficacy and safety of Sparlon. We hope to be able to show you with our data today that not only is Sparlon effective for the treatment of ADHD, but

it has also been shown to be acceptably safe for the treatment of ADHD in pediatric patients.

[Slide]

We have also been asked to address the dermatological safety of Sparlon tablets. Just by way of orientation, this slide represents cases of SJS in pediatric patients in clinical trials as well as in our postmarketing experience. Other speakers are going to go into this in much more detail. This is just to orient you that an earlier review by our experts indicted that there was one case of probable SJS in our clinical trial program out of 1622 patients exposed. However, that case is of uncertain etiology. In addition, if the committee has questions or interest in the clinical course of that patient, we do have the investigator here at the meeting today who can describe the clinical course of that patient.

In our pediatric postmarketing experience we have seen no pediatric cases of SJS in over 30,000 pediatric patient-treatment years.

[Slide]

We will have a number of presentations today, beginning with an overview of attention deficit hyperactivity disorder by Dr. Joseph Biederman. That will be followed by a review of both the clinical pharmacology and efficacy by Dr. Lesley Russell. Dr. Srdjan Stankovic will then provide an overview of the safety and then Dr. Russell will conclude with an overall benefit-risk assessment.

[Slide]

We have a number of consultant experts in the field with us today representing various disciplines including psychiatry/ADHD, dermatology, addiction medicine, cardiology, child development as well as epidemiology. I would just like to highlight one name since dermatology is a major issue in today's presentation, we do have an individual, Dr. Neil Shear, with us today who has published extensively in peer reviewed journals on SJS as well as other dermatological disorders. I would also like to note, as you can see on this slide, that we have a number of investigators with

us today.

[Slide]

With that, I would now like to introduce Dr. Joseph Biederman, who is professor of psychiatry at Harvard Medical School. Dr. Biederman?

Overview of ADHD

DR. BIEDERMAN: It is a pleasure to be here. I would like to offer you a very brief overview of ADHD as a very serious illness of genetic etiology affecting the brain that has a bad prognosis. I strongly believe that without understanding the assessment of benefit-risk alternative treatment is impossible.

[Slide]

First of all, I think that it is important to note that ADHD is a highly heterogeneous illness like all psychiatric illnesses. We know that genes are important, as I am going to show you in moment--perhaps the most important risk factor. We know quite a bit about heterogeneous neuroanatomy and neurochemistry. We know that CNS insults, if

affecting key regions of the brain like the prefrontal cortex, can produce very similar problems as those produced by genes. Even environmental factors can be important in ADHD. We need to consider that environmental factors are not bad mothers or bad teachers, like frequently thought, but include things like poverty, exposure to parental psychopathology, etc., etc., things that in themselves can be driven by genes. So, heterogeneous illness requires different treatment. Different patients require different alternative therapeutic options.

[Slide]

Another thing that has been highlighted today but I would like to stress again is that ADHD is a worldwide condition, not only an American invention. It affects children in the 5-10 percent range worldwide. Data are coming from Asia now, from China and Japan and data from South American, Western and Eastern Europe and, of course, North and South American point to the fact that no matter what criteria you want to use, it is an

extraordinarily common disease. You have to remember that at least 50 percent--at least 50 percent of the children of today are going to be adults tomorrow and we now know that ADHD affects at least 4 percent or 5 percent of adults in this country, not only that it affects them but it is very morbid and dysfunctional.

I would like to stress that the yardstick of considering the severity of an illness just by mortality may not be an adequate yardstick. Many conditions are devastating to our patients, even though they are not necessarily lethal in the traditional sense, like malignancies. This is a condition that profoundly affects the lives of those affected and everybody around them.

[Slide]

Many of the MRI studies that have been conducted have been small and many of the children participating in them have been medicated, creating the suspicion that perhaps what we see in MRI studies may reflect the toxic effects of medications. Therefore, this study that I briefly

want to review for you is extraordinarily important. This study is large. It was published in a very prestigious medical journal, JAMA. It was done by colleagues at the National Institute of Mental Health. The lead author is Dr. Castellanos. And, 152 children and adolescents of both genders and a similar number of controls of both genders were assessed longitudinally. The specific objective of the study was to assess the issue of medication status, whether medication is important in brain abnormalities.

[Slide]

What this study found is that the brain of children and adolescents with ADHD was significantly smaller, in the 3 percent range, independently of medication status. These volumetric abnormalities were persistent over time so this is not a neurodegenerative disease. It is early disease that persists into adult life. There were no gender differences and there was some evidence of an association between severity of ADHD and brain findings.

[Slide]

The visual of this study shows the brains--these are males up to the age of 20; females out to age 15. You can see that both genders have significantly smaller brains and the lines are flat over time.

[Slide]

The conclusion of this study is that either genetic or early environmental influences on brain development are operant in ADHD. These are fixed, nonprogressive and unrelated to stimulant treatment.

[Slide]

If you look at key regions of the brain that are involved in attention and executive function, anyone of us in this room irrespective of having or not having ADHD, we have this area of the brain--this is the cingulate gyrus; this is the dorsal anterior cingulate associated with executive control; dorsolateral prefrontal cortex associated with selective attention; and the right frontal lobe associated with alerting. These are

interconnected areas, key regions for cognition and attention. Their disruption will cause symptoms of ADHD.

[Slide]

This is a recent study that we just submitted for publication from our program at the Mass. General. This is a three-dimensional reconstruction of the anterior cingulate. What you see here is a study of adults with ADHD. The anterior cingulate area is 13 percent smaller in individuals with ADHD compared with controls.

[Slide]

With imaging studies you can do not only volume, as I just showed you with the three-dimensional reconstruction so you can measure volume of this region--this is the cingulate gyrus again--but you can also measure the thickness of the cortex, how thick or thin is the cortex in critical brain regions.

[Slide]

So, this is another study that we have done in our program of cortical thickness. This

has not yet been published but I promise you it will be published. What you see, first of all, in red here is a statistical comparison between the brains of ADHD individuals compared with controls. What this depicts, in orange and yellow, is significant differences in cortical thinness. These areas are selectively thinner in these regions. So, you don't see thinness across the entire brain; you see thinness in critical cortical regions involved with executive control and attention. This is the dorsal anterior cingulate. This region hovers between the cognitive and emotional division of the anterior cingulate--very important issues for clinical understanding of the symptoms of this condition. This is, of course, the dorsolateral prefrontal cortex that is clearly involved in cognition and in the symptoms that subserve this illness.

[Slide]

We have also done this analysis. It is very exciting. This is diffusion tensor imaging that measures white tracts. What you see here is

that we are documenting disruptions in the perigenual area of the anterior cingulate and dorsal anterior cingulate selectively. So, this area of the brain that is involved in cognition, executive functions and regulatory controls is smaller in volume, is thinner in cortical thickness and has other abnormalities as well. I am not aware of many other psychiatric illnesses can claim such conversion of information, focusing on the same brain regions that could certainly account for the clinical picture.

[Slide]

If you look at functional MRI in the same region, if you look at the coronal view of the brain, if you put people without ADHD on the scanner you can very nicely activate anterior cingulate doing a very mild cognitive task. If you put adults with ADHD, they fail to activate the same region and, instead, they activate insular so these adults can do the task but they are not using the part of the brain that is specifically wired to do the task at hand. We have very exciting new

data that you can correct this malfunction with medications.

[Slide]

These findings on neuroimaging are extraordinarily congruent with conceptualization from neuropsychology. As you know, ADHD is considered a neuropsychological disease. What is called directed attention, the circuit that allows people to pay attention to things that they are not interested in is disrupted. Inhibitory deficits, the person fails to inhibit when destructions occur; and executive dysfunction issues of planning and organization, working memory, etc., etc. are disturbed. These are the regions that are in this part of the brain where we are documenting abnormalities.

Another circuit that is involved in ADHD is called fascination reward circuit. People with ADHD have difficulties with delayed gratification; difficulties with regulating mood. This kind of hot temper that characterizes people with ADHD and some of the road rages that lead to accidents, and

so on and so forth, may be accounted for by these neuropsychological deficits.

[Slide]

Another key aspect to document that ADHD is a neurobiological disorder is genetic research. ADHD clearly runs in families. There is a 5-7-fold increased risk of ADHD in first-degree relatives of children with ADHD. Of course, that is not evidence for genetics so we need to have additional information to make a genetic hypothesis or genetic claim. Twin studies are very important because twins come from two varieties, monozygotic and dizygotic twins. For genetic illnesses, you expect that monozygotic twins will have a higher level of concordance than dizygotic or fraternal twins.

Twin studies are also very important because they can allow us to compute coefficients of heritability that I will tell you about in a moment. Adoption studies are important because with genetic illness you expect to have a higher rate of the disease in biological rather than adopting relatives. Finally, molecular genetic

studies will look at specific genes that may be associated with this condition.

[Slide]

Coefficients of heritability are based on twin studies. I would like to point out to you that there are a lot of twin studies in ADHD. Coefficients of heritability range from zero/zero percent of the variance accounted for by genes to 100/100 percent of the variance accounted for by genes. The congruence of the genetic studies for the coefficient of heritability in ADHD is remarkable. Even though the studies use different methods, parent support, teacher support, structured interviews questionnaires, look how consistent this is. On average, coefficients of heritability are close to 80 percent, in other words, 80 percent of the variance of ADHD can be accounted for by genes. For example, height, a very genetic trait, is about 90 percent genetic; schizophrenia and bipolar illness, very genetic. Recognized genetic illnesses are equally genetic as ADHD, 80 percent. Panic disorder and major

depression are genetic as well, about 50 percent, 0.5 for coefficient of variability; other medical conditions like asthma or breast cancer at 0.3, 0.4 coefficients of heritability. So, we are dealing with a very genetic brain disorder here.

[Slide]

Specific genes have been associated with ADHD. The first genes that were looked at in ADHD are genes that are associated with the dopamine system, candidate genes because the drugs that we usually use to treat this condition are dopaminergic drugs. Mutation in a dopamine transporter gene, what is called DAT1 or DAT10; mutation in the dopamine receptor of D4 and D5 genes--these are cortically distributed receptors. There is also an association between a very rare thyroid disease on chromosome 3. People that have this mutation also have ADHD, but this probably accounts for very little of ADHD out there.

[Slide]

So, the genes that have bee associated with ADHD in a consistent fashion are the dopamine

transporter genes that bring back dopamine to the presynaptic neuron. This gene over-expresses the dopamine transporter, make more it active or more transported, too much dopamine to the presynaptic neuron. Cortically distributed genes are the D4 and D5. There is also a gene, SNAP25, that is involved in the presynaptic encapsulation of dopamine.

[Slide]

Well, I see this slide is totally degenerated. I am very sorry. But what I would like to say is that Dr. Faraone published in Biological Psychiatry a review of a meta-analysis. There are certain genes, about seven genes that consistently have been associated with ADHD, several genes in the serotonergic system, DBH, dopamine transporter gene and also dopamine receptor DR D4 and DR D5. These genes have been found in multiple studies in meta-analyses of these specific genes to be associated with ADHD. You probably have these details in the handout, as well as the reference for the paper that support these

claims.

[Slide]

The treatments that we have available are clearly effective. This study was not done by industry. It was funded by the NIMH on the multi-modal treatment of ADHD. This study studied close to 600 children 7-9 years of age in this country, in 5 sites. This was a study in which children were randomized to very aggressive medication management, very aggressive, comprehensive behavioral treatment, a behavioral treatment that was so comprehensive that you could not possibly improve on it, and it is so expensive that it is not doable. But that was the purpose of the study. Children received both medication and behavioral management and community-based treatment.

[Slide]

What this study found, and I would like to point this out to you, is that these two arms, the very aggressive medication arm and combination treatment were superior to just behavioral

treatment and community based treatment that consisted largely of communication too. This group, here, is a group that received the best treatment that we can offer, very aggressive pharmacotherapy and very aggressive behavioral treatment. And, even using the best we can, the response is 60 percent, leaving 40 percent of our patients inadequately treated with intolerable side effects or with difficulty tolerating this treatment.

[Slide]

Stimulants are Schedule II drugs. About 40 percent or perhaps more do not tolerate or to not respond to these treatments. The side effect profile of sleep, appetite, difficulties with mood and anxiety can seriously hinder our ability to treat all the patients that otherwise could benefit, and concerns about growth suppression and tic development continue to plague stimulant treatment in ADHD, Although the data is generally reassuring, people continue to be concerned about these issues.

[Slide]

ADHD not only affects school and school performance, it is clearly a life disease. For example, ADHD has been shown to be associated with a significantly increased risk for automobile accidents, and automobile accidents, as you know, are the leading cause of death in our young. So, patients not only have poor grades in school or may not reach college but may not reach adult life altogether or may kill somebody in the process of driving and not paying attention to the road.

[Slide]

So, if you look at the morbidity of ADHD as a serious--perhaps not a lethal illness but a very devastating illness to the individual, the family and society secondary to under-achievement, under-employment, marital difficulties, drugs and substance abuse, legal difficulties, or morbidity, we are dealing with an extraordinarily morbid disease that can profoundly affect those afflicted with this condition.

[Slide]

So, in summary, ADHD is a neurobehavioral disorder with complex etiology. It is a disorder that affects the brain; has a strong genetic component, as I alluded to; affects millions of people worldwide, both sexes. It is highly persistent in the majority of those affected. It has a negative impact on the life of the individual affected and everybody around. Although the stimulants are clearly an effective treatment for ADHD, a sizeable number, in the order of magnitude of 40 percent, are non-responsive or not tolerating this treatment, calling for alternative treatment for this condition. Thank you very much for your attention.

[Slide]

The next presentation will be by Dr. Lesley Russell who will be talking about clinical pharmacology and efficacy.

Clinical Pharmacology

DR. RUSSELL: Thank you, Dr. Biederman.

Today I would like to briefly overview the clinical pharmacokinetics of modafinil in children,

and then summarize for you the efficacy findings of our program in ADHD.

[Slide]

Just to begin with, here is an outline of the development program that Cephalon undertook in children and adolescents with ADHD. The three Phase 3 studies, studies 309, 310 and 311, formed the basis of the efficacy and safety that will be discussed today. In addition, we had two pharmacokinetic studies, studies 113 and study 206, that outline the pharmacokinetic parameters of modafinil in children. In addition, we conducted two studies, 207 and 213, to help us define the dose required for the Phase 3 studies. All patients in the Phase 3 studies and some from the Phase 2 studies were allowed to enroll into study 312 which is an ongoing open-label extension program. Following submission of the sNDA, we initiated a further study, study 3044, in which 303 patients were enrolled. This study is still ongoing.

[Slide]

I would now like to briefly summarize the pharmacokinetics of modafinil in children.

[Slide]

As shown on this slide, the pharmacokinetics and exposure are dose-proportional over the dose range studied. The absorption is rapid, with a maximum concentration observed 2-3 hours after administration. When administered with food, there is an approximate 1 hour delay in the time to Cmax although the overall absorption is not affected. The volume of distribution increases in children linearly with their weight. The metabolism of modafinil is primarily hepatic, with less than 10 percent excreted unchanged in the urine. There are 2 primary metabolites, modafinil acid and modafinil sulfone. As you heard earlier, we did observe higher levels of modafinil sulfone in the younger children. The elimination of modafinil is time- and age-dependent. We observe a decrease in clearance over time with steady state being reached by about week 6 of treatment. There is a gradual decrease in clearance with age, with a

pronounced shift between 9-11 years of age. So, we see that there is a half-life in the younger children of approximately 7 hours which is compared to a half-life of 15 hours in the adults.

[Slide]

I would now like to outline for you the basis of the dose selection that we used in the Phase 3 studies. Study 207 was a relatively small, double-blind, randomized, 4-period crossover study, and this was the first program undertaken to assess the efficacy of modafinil in the treatment of ADHD.

The results shown for you are the total scores on the ADHD rating scale as assessed by the parent. With the caveats of this being a small study, you can see that those patients who received 100 mg barely discriminated from placebo. A slightly larger treatment effect was seen with the 200 mg dose group and a larger treatment effect was seen with the 300 mg or 400 mg dose group. And, I should reiterate here that the 300/400 mg doses were administered based on weight, with the 300 given to children less than 30 kg and the 400 to

those children weighing at least 30 kg or more.

[Slide]

The next study we undertook was study 213, and this was designed to see the best way of administering a single dose of 300 mg either as a single dose administered first thing in the morning, which is depicted in blue, or as a split dose of 200 mg in the morning and 100 mg at lunch, depicted in orange, 100 mg in the morning and 200 mg at lunch time, depicted in pink and compared to placebo.

As you can see from the slide, there appeared to be little benefit to splitting the dose and the largest response we saw was in the 300 mg dose group administered as a single dose. As you can see on the right-hand side of the slide, this is for all patients, but when we looked at it stratified by weight you can see that it is clearly the younger and lighter children that had the larger response. So, from this study we concluded that older and heavier children may require a higher dose.

[Slide]

This slide identifies the systemic exposure that we saw following these dosing regimens. In the middle, here, are those children weighing less than 30 kg who received 300 mg. Here are those children weighing more than 30 kg who received. You can see that the systemic exposure associated with the lighter children is clearly higher than the systemic exposure with the heavier children.

[Slide]

Using these data and the clinical efficacy results from the Phase 2 studies, we developed a pharmacokinetic/ pharmacodynamic model and estimated that the systemic exposure which would be associated with a consistent pharmacodynamic effect would be in the order of 150 mcg/hour/ml, and that the doses that would be required to achieve this exposure at steady state would be 340 mg for those children weighing less than 30 kg and 425 mg for those children weighing 30 kg or more.

[Slide]

Following the Phase 3 program which included sampling from population pharmacokinetics, we went back to test this hypothesis. As you can see from this slide, we pretty much got it right in that here are the children weighing less than 30 kg who received 340 mg and here are those heavier children who received 425 mg, and the systemic exposure in those groups is pretty similar, around 150 mcg/hour/ml. As you will see from the next slides, these doses were associated with substantial efficacy.

[Slide]

Here are the designs of the 3 pivotal studies that were undertaken. All studies were double-blind, randomized, placebo-controlled and had a 2:1 randomization. Study 309 and 311 were identical in design. Both were 9 weeks in duration and employed a flexible dose titration regimen whereby children could be titrated from a minimum dose of 170 mg to a maximum dose of 425 mg based on perceived efficacy and their tolerability to treatment. The dosing increments occurred on a

weekly basis at 85 mg.

Study 310 was slightly different. This study had a 7-week efficacy period and a 2-week period that assessed abrupt discontinuation of the drug, the results of which I will not show you today. This study was also a fixed dose study and patients were titrated at 85 mg increments every 2 days to their target dose based on weight, so 340 mg for the children weighing less than 30 kg and 425 mg for those children weighing 30 kg or more.

[Slide]

The patients enrolled in the study were very similar. All patients were 6-17 years of age with a diagnosis or ADHD according to the Diagnostic and Statistical Manual of Mental Disorders. The children were required to be at least moderately ill on the Clinical Global Impression of severity and have an ADHD rating scale which was at least 1.5 standard deviations above the norm for age and gender. Patients were required to be of normal intelligence with no learning disability and attend school full time.

Patients were excluded from study if they failed to respond to 2 or more adequate courses of stimulant therapy, although it should be noted that patients who had failed one stimulant therapy were allowed to be enrolled. Patients were also excluded if they had psychiatric comorbidities requiring current pharmacotherapy and were well controlled with their current ADHD therapy and had no good reason to change treatments.

[Slide]

The efficacy assessments were identical for each of the 3 studies. The primary outcome measure was the change from baseline in the Total Score ADHD Rating Scale as assessed by the teacher.

Secondary outcome measures included a change from baseline in the Home ADHD Rating Scale as assessed by the parents in the evening between 6:00 and 8:00 at night; the Clinical Global Impression of change as assessed by the treating physician; the Conners' Parent Rating Scale as assessed by the parent; the test of Variables of Attention, which is a continuous performance test;

the Social Skill Rating Scale and the Child Health Questionnaire.

[Slide]

As you can see, the average age of patients entering into the program was around 10, with the majority of patients being less than 12 years of age. The majority were boys and white, and about two-thirds of the patients actually weighed 30 kg or more.

[Slide]

As per inclusion criteria, patients were required to be at least moderately ill on the Clinical Global Impression of severity and, as you can see from the slide, about 50 percent of the patients were considered to be moderately ill and the other 50 percent were considered to be markedly or severely ill. Around two-thirds of the patients had the combined inattentive and hyperactive subtype of ADHD. About a third were predominantly inattentive and very few were purely hyperactive. The baseline ADHD rating scale at entry was on average 37, which is well above the norm for a

10-year boy which is roughly 18.

[Slide]

A total of 638 patients were randomized into the study and 630 received treatment, 420 in the modafinil treatment group and 213 in the placebo treatment group. Around two-thirds of the patients completed the double-blind treatment period, with the reasons for discontinuation outlined here. As you can see, some of the main reasons for discontinuation were lack of efficacy with a much higher proportion in the placebo treatment group, and adverse events with the higher proportion in the modafinil treatment group. The other reasons are listed for you here.

[Slide]

The following three slides will show the outcomes of the primary efficacy variables for each individual study. Here are the results for study 309, the first of the flexible dose studies. Just to orient you, on the Y axis is the Total ADHD Rating Scale with the lowest score showing benefit, and across the X axis is the duration of the

treatment period in weeks.

Just as a reminder, the primary outcome variable was the change from baseline to endpoint using the last observation carried forward analysis. As you can see from this slide, there was a statistically significant difference in favor of those patients being treated with modafinil. More specifically, the treatment effect on the modafinil treatment group was 17.5 points with the treatment effect on the placebo group of 9.7 points for an effect estimate, which is the difference between the 2 treatment groups using the Lee squared means of 7.4. In addition, statistically significant results were seen using the observed cases analysis.

[Slide]

A similar result was seen in study 311 which is the second flexible dose study. At endpoint the treatment effect on the modafinil treatment group was 15 points and a treatment effect on the placebo group was 7.3 points for an effect estimate of 8. Again, this is statistically

significant both at endpoint and using the observed case analysis.

[Slide]

The last study is study 310 and, again, a very consistent treatment effect was seen in this study, with a treatment effect of minus 17.2 points on the modafinil group versus 8.2 points on the placebo treatment group for an effect estimate of 9.

[Slide]

Outlined for you on this slide is just another way of viewing the data. On the left-hand side of the screen is the modafinil treatment group at baseline and at endpoint. On the right-hand screen is the placebo group at baseline and at endpoint. This slide illustrates the remarkably consistent effect seen not only in the modafinil treatment group but in the placebo treatment group. The red line depicts what would be considered to be a normative value on the ADHD rating scale for a 10 year-old boy. As you can see, those patients treated with modafinil are beginning to approach

this normative value.

[Slide]

We also assessed the effect of treatment using a responder analysis on the School ADHD Rating Scale with those patients who had at least a 30 percent reduction in their scores from baseline to endpoint or a 50 percent reduction from baseline to endpoint. As you can see, in all 3 studies a significantly higher proportion of patients treated with modafinil had either a 30 percent or a 50 percent reduction in their ADHD symptoms.

[Slide]

This slide shows for you in all 3 studies the home version of the ADHD Rating Scale. As a reminder, this was assessed by the parents in the early evening. The results seen here very much mirror the results we saw using the school version of the ADHD Rating Scale, with significant differences seen both at endpoint and in the observed case analyses in all 3 studies in favor of the modafinil treatment group.

[Slide]

Depicted here is the responder analysis on the Clinical Global Impression of improvement. Outlined for you are those patients who were either considered to be much or very much improved by the treating physician. Again, in all 3 studies we see a very consistent treatment effect, with a significantly higher proportion of patients considered to be much or very much improved on this scale by the treating physician.

[Slide]

Another commonly used scale for assessing ADHD and their response to medication is the Conners' Parent Rating Scale. Again, you can see in each of the 3 studies, using this scale, a very similar effect to the observation seen using the ADHD rating scale, with improvements on the modafinil treatment group in cognitive problems and in attention, hyperactivity and their total ADHD index.

This scale also allows the assessment of treatment on the oppositional behavior. As you can see, in all 3 studies there appears to be a

treatment effect in favor of modafinil, although this is only statistically significant in study 311.

[Slide]

The one inconsistent effect that we saw was using the Test of Variable Attention. Outlined for you in this study is the pooled analysis using data from all 3 studies. Although you can see that those patients treated with modafinil tend to do better than those patients treated with placebo, it should be noted that this is actually a decline in performance rather than an improvement in performance over time.

[Slide]

Children with ADHD often have poor peer to peer relationships and difficulties with socialization. We wanted to assess the effects of treatment on these parameters and we used the Social Skills Rating Scale. Again, this is the data from all 3 studies pooled. The individual studies did show a consistent treatment effect. As you can see, there appears to be an improvement in

many of these parameters when treated with modafinil, including the Social Skills Total Scale.

[Slide]

A similar improvement was seen in other problem behaviors as measured by this scale. It should be noted that these results were only seen in the children in grades kindergarten to 6th grade and we observed no major differences between treatment groups in the older age groups.

[Slide]

Lastly, here are the results of the Child Health Questionnaire, a global sort of quality of life instrument that assesses many behaviors that can be impaired with ADHD. Again, this is the pooled analysis of all 3 studies. As you can see from this slide, there appears to be an improvement in many of the behavioral aspects seen for those patients treated with modafinil--

[Slide]

--including an improvement in the total psychosocial summary. We did not see significant improvements in the physical functioning domain,

although it should be noted that these values were normal at baseline.

[Slide]

We have undertaken many subgroup analyses, many of which are outlined in your briefing document. Here I just want to show for you the subgroup analysis for those patients who were either stimulant naive at study entry, and that was for about 50 percent of the patients, and those patients who had received a prior stimulant before enrolling into the study, which was again about 50 percent of the patients.

Here you can see that treatment with modafinil was effective even in those patients who had had prior stimulant therapy, although it should be noted that the treatment effect appears to be larger in those who were stimulant naive.

[Slide]

In conclusion, we saw consistent efficacy results across 3 pivotal studies. The improvement in ADHD symptoms was seen by the teachers, the parents and the treating physicians. Improvements

were seen at school, at home and across the day. As well as improvement in the core ADHD symptoms, we did observe improvement in other psychosocial domains. Finally, we saw efficacy in stimulant naive patients and in patients who had had prior stimulant experience.

[Slide]

I would now like to hand over to Dr. Srdjan Stankovic who will outline safety for you.

General Safety

DR. STANKOVIC: Thank you. My name is Serge Stankovic and I am with the Cephalon clinical research group.

[Slide]

My presentation this morning on modafinil safety is organized as follows: I will review overall modafinil exposure in clinical trials. Following that, I will review the safety data for the modafinil ADHD program in children and adolescents, and this will include review of general safety and events of special interest such as skin reactions and psychiatric events. In the

balance of my presentation I will briefly summarize high level safety information from our development program in excessive sleepiness in pediatric patients. Finally, I will review modafinil information coming from our postmarketing safety surveillance.

[Slide]

Overall, safety data for 933 patients with ADHD were included in the supplemental NDA, submitted in December of 2004. Of these, in the 3 Phase 3 placebo-controlled trials, 420 patients were treated with modafinil and 213 patients were treated with placebo. Please note these numbers as I will often refer back to them when I am presenting data from our controlled trials.

Following the sNDA submission, one additional open-label study in children with ADHD was initiated. With that, as of February, 2006, a total number of pediatric ADHD patients exposed to modafinil was 1236. Additional pediatric exposure comes from our development program in excessive sleepiness, 270 pediatric patients, and from

pediatric patients exposed to a variety of foreign studies for various indications, 116 patients.

Finally, just a reminder that 4000 adult patients were exposed to modafinil in the development program for excessive sleepiness and in other clinical trials.

[Slide]

Looking at patient exposure in the pediatric ADHD program, this slide presents exposure by modal dose and duration for 933 patients as of February 1, 2006. A total of 246 patients were treated with modafinil for a minimum of 12 months, and as many as 164 were on drug for 18 months or longer. About half of the patients received modafinil at the modal dose of 425 mg a day, while about one-third at the modal dose of 340 mg a day. The total exposure to modafinil in the pediatric ADHD program is 575 patient-years.

[Slide]

Next I will discuss adverse events observed in ADHD studies of children and adolescents.

[Slide]

A general overview of adverse events reported in 3 Phase 3 placebo-controlled studies is presented on this table. While the majority of patients in both groups experienced at least one adverse event, a higher incidence was observed in the modafinil treatment group. Relatively few of these events were reported to be severe, were reported to be a reason for study discontinuation or were reported to be a serious regulatory definition of that word.

[Slide]

The most commonly observed adverse events in the Phase 3 placebo-controlled studies were insomnia, headache and anorexia. The COSTART term of anorexia used here includes both loss of appetite and decreased appetite. In fact, about 70 percent of patients reporting anorexia experienced decreased appetite. Insomnia and anorexia were reported at a substantively higher rate in the modafinil group compared to placebo. Review of these two events indicated that very few were

reported as severe, specifically 9 out of 115 events for insomnia and 1 event for anorexia. Likewise, only 5 events in insomnia led to discontinuation, while 2 patients reporting anorexia discontinued study due to that adverse event. In most instances, these 2 events first occurred in the initial 2 weeks of treatment and the median duration reported was about 2 weeks.

[Slide]

Out of 933 patients included in the sNDA, 18 patients experienced at least one serious adverse event by the time of the 10-month safety update submitted in November of 2005. Four of these patients were enrolled in the 3 placebo-controlled Phase 3 studies and all of them were in the modafinil treatment group. From the 2 ongoing pediatric studies in ADHD, 3 patients experienced a serious adverse event during the period up to February, 2006. Discussion of serious skin adverse events as well as psychiatric events in more detail with be part of the discussion of special safety.

[Slide]

In the next four slides I will review relevant information related to laboratory evaluations from the pediatric ADHD studies. Data for selective hematology and blood chemistry parameters will be reviewed in more detail. Although included in your background package, data for other laboratory parameters did not raise questions or concerns and, therefore, will not be presented here today.

[Slide]

Based on some early observations from the Phase 2 studies, concern was raised regarding modafinil treatment effects on absolute neutrophil count and white blood cell count in children. Our Phase 3 controlled data did not show a meaningful difference in mean change from baseline or incidence in clinically significant values between modafinil and placebo. Furthermore, as presented on this slide, when the lowest on treatment values are grouped by range there was no meaningful difference between modafinil and placebo treatment

groups.

[Slide]

With respect to serum chemistry, as in adults, we did observe a difference in mean change from baseline between modafinil and placebo for alkaline phosphatase and GGT. In the Phase 3 placebo-controlled studies there were few patients experiencing a clinically significant change on any of the parameters, with no apparent imbalance between treatment groups. On the next slide we will discuss LFT elevations highlighted in the background document as cases of possible concern. These cases are included in this table in the column for all modafinil studies.

[Slide]

In the FDA approvable letter it was stated that although controlled trials data did not reveal a signal for drug-related mean increase in transaminase values or in drug-related outliers, there were 3 modafinil-treated patients who had transaminase increases of concern, but insufficient other information to further assess the

significance of these changes. Details related to these 3 patients are presented on the slide.

In all 3 cases, total bilirubin values both at the time of observation of abnormal LFT values and throughout the study were normal. In one case laboratory abnormalities returned to normal while patients continued treatment with modafinil. In the second case treatment was continued for an additional 6 months prior to study discontinuation. At that time, all abnormal LFT values returned to normal except for a mild elevation in ALT. In the third patient abnormal values returned to normal after withdrawal of modafinil. This case will be discussed later in relation to possible hypersensitivity reactions.

[Slide]

The next segment of the safety presentation is focused on cardiovascular safety. I will review blood pressure and pulse data, ECG information including QTc interval and cardiovascular adverse events from the Phase 3 placebo-controlled trials. It should be noted that

the vital signs measurements in ECGs were recorded in these studies at variable time points during the day and in relation to the intake of study medication.

[Slide]

With respect to blood pressure, no notable effects in sitting blood pressure were observed in the Phase 3 controlled studies. Presented on this slide are box plots for systolic blood pressure on the left side of the screen and diastolic blood pressure on the right side of the screen in modafinil and placebo treatment arms respectively.

Changes from baseline for both systolic and diastolic blood pressure were similar in the 2 treatment groups with respect to both mean values, overall distribution and extreme outliers.

[Slide]

This graph presents the distribution of observed change from baseline in sitting pulse for the 2 treatment groups. As presented, we observed similar distribution between the 2 treatment arms and the occurrence of outliers.

[Slide]

Review of the ECG tracings from the ADHD pediatric studies did not reveal specific concerns both with respect to morphology or interval measures. This slide presents an overview of QTc interval data from the 3 placebo-controlled trials expressed as maximum change from baseline or as maximum duration observed. The slide presents data for QTc using the Fridericia correction, but the findings are similar when other corrections are used. Either way, there is no apparent effect on QTc interval or imbalance between treatment arms.

[Slide]

Finally, when reported adverse events are reviewed, we observe relatively few cardiovascular events. Only a small fraction of these, 2 patients on modafinil and 1 on placebo, reported events leading to treatment discontinuation. In all 3 cases the stated reason for discontinuation was tachycardia. None of the reported cardiovascular events were reported to be serious.

[Slide]

Important consideration in the safety evaluation of any ADHD compound is assessment of its effects on growth. [Slide]

In the placebo-controlled Phase 3 studies modafinil treatment of up to 9 weeks duration led to relative weight loss compared to weight gain observed in the placebo group. Similarly, a significantly higher proportion of modafinil-treated patients experienced clinically significant weight loss, defined as at least 7 percent in weight reduction. To be precise, 9 percent of modafinil-treated patients versus 1 percent of placebo-treated patients experienced significant weight loss during the study.

[Slide]

Naturally, we did look at the longer term treatment data related to weight and growth in general. As you know, for accurate evaluation of growth effect in children, we need to evaluate them relative to norms. To achieve this, we expressed changes in weight and height using Z-scores. Just a quick reminder, Z-score is a statistical measure

that quantifies the distance measured in standard deviations of a patient data point, in this case individual weight or height, from the population mean, in this case CDC growth norm for corresponding age and gender.

This graph presents mean weight and height Z-scores over 12 months of treatment with modafinil. A decline in Z-score is observed initially in the first 3 months of treatment consistent with the reported weight loss in our short-term trials. In the following months the line remains horizontal, meaning that the normative pattern of growth is regained. Using the same presentation, it is apparent that there was no indication of adverse effects on height over the 12 months of treatment with modafinil.

[Slide]

In the course of the modafinil ADHD pediatric development cases of serious skin reactions were reported. Some of these were indicative of a possible Stevens-Johnson syndrome or hypersensitivity reaction, generally a rare but

very serious complication of treatment. Cephalon shares the important concerns raised by our colleagues at FDA in regard to these events. Therefore, I will review skin events in greater detail.

[Slide]

To bring everybody on the same page with respect to cases of interest, I will start with the list of events, included in the FDA briefing document, in the second dermatology consult report dated February 27, 2006. In this report the events were grouped in 3 categories based on the level of diagnostic confidence. The 3 groups are events representing EM, SJS or TEN; events somewhat suggestive but lacking confirmation; and events resembling prodromal presentation but without sufficient information for diagnosis. Cephalon has performed a similar review and in the next two slides I will review cases from the first two groups. With respect to the third group, our review did not support the conclusion that any of these cases should be classified as SJS or

prodrome. We based this on the low specificity and low predictive value of reported symptoms. Additionally, many of the symptoms are quite common and many were not reported concomitantly or concurrently.

[Slide]

First, we will review the clinical trial cases. Patient number 1 is a 7 year-old boy who, on day 16 of treatment with a 340 mg dose, presented with symptoms described by the investigator as erythema multiforme, Stevens-Johnson syndrome and both FDA and Cephalon reviewers agreed that the diagnosis of Stevens-Johnson syndrome is likely accurate, with less consensus on the possible etiology. I am sure that this case will be discussed in more details later and, as Dr. Raczkowski said, we have the investigator here who was treating the patient, as well as members of our panel of dermatologists who can talk more about the case.

Patient number 2 is an 11 year-old girl reported with morbilliform rash on day 15 with

treatment of a 200 mg dose of modafinil. This patient was hospitalized and the SJS diagnosis was excluded. FDA review indicated that this was a case representative of EM/SJS. Cephalon's panel of independent reviewers, on the other hand, was unanimous that the reported diagnosis of morbilliform rash is probably correct and the event did not represent Stevens-Johnson syndrome.

Patient number 3 is a 6 year-old boy who reported rash, fever and vomiting 2 weeks after initiation of treatment. Review of the source documentation received from the investigator indicated that this event was diagnosed as fifth disease.

Patient number 4 is an event in an 8 year-old boy described as rash on the cheeks and blisters on the lips, and was reported as erythema multiforme. The event occurred on day 23 of treatment with a 300 mg dose of modafinil. This case is considered by the FDA reviewer as somewhat suggestive but not representative of EM/SJS or TEN. Cephalon's reviewers, on the other hand, agreed

that this is unlikely erythema multiforme, but did not agree on the alternative diagnosis. One considers this event to be possible SJS. A second reviewer considered it to be probable herpetic gingivostomatis and a third independent reviewer attributed to the event as either viral etiology or SJS.

Patient number 5 is a 9 year-old boy with reported symptoms of urticaria, fever and facial edema. This patient also had elevated transaminases. Cephalon's review indicates that this is a possible case of hypersensitivity reaction and it is not consistent with SJS.

[Slide]

In the review of postmarketing reports both FDA and Cephalon concluded that there were 4 reports of serious skin reactions, 1 SJS/EM and 3 SJS reports. Of the 12 suggestive but not confirmed cases on the FDA list, Cephalon has identified 8 reports considered suggestive of possible hypersensitivity but not indicative of EM, SJS or TEN spectrum. The other 4 cases were also

not considered suggestive of SJS.

[Slide]

In the Phase 3 placebo-controlled trials the incidence of rashes coded by the COSTART coding system was 4 percent in the modafinil treatment group and 2 percent in placebo. As we all know, the preferred term "rash" in the COSTART coding system does not include many terms that could be considered non-urticarial rash. Therefore, Cephalon undertook an additional analysis to ascertain the incidence of non-urticarial rash. In collaboration with 2 external dermatology experts, we defined a category of non-urticarial rash which included all adverse events indicative of rash, excluding urticaria and related reactions.

Using this definition, cases of non-urticarial rash in the pediatric ADHD studies, as well as in the pediatric studies for excessive sleepiness and in all adult studies with modafinil were identified and frequency tables were constructed. Additionally, all reported adverse events of urticaria, hypersensitivity reactions and

all allergic reasons in the pediatric ADHD studies were reviewed for possible underlying causality and prior medical history.

[Slide]

Based on the described methodology, we calculated the incidence of non-urticarial rash across treatment groups in controlled pediatric ADHD trials and in all pediatric patients. This table presents the incidence in the placebo-controlled trials. We also present the incidence of those described as severe and those leading to treatment withdrawal. The overall incidence of rash was higher in the modafinil treatment groups, with few being described as severe or leading to treatment discontinuation.

[Slide]

In the ongoing open-label study in ADHD initiated after the supplemental NDA submission a total of 303 additional newly exposed patients entered the study, with 188 receiving modafinil for at least 4 weeks. Presented on this slide is the observed incidence of non-urticarial rash in that

study. As in the previous slide, we also present the incidence of events described as severe or those leading to discontinuation.

As seen on this slide, the reported incidence is somewhat lower compared to the modafinil group in the controlled studies. One patient reported a severe rash on day 10 and discontinued the study on day 13 due to this rash which was described by the investigator as rash.

[Slide]

The overall incidence of non-urticarial rash reported in the controlled pediatric studies for excessive sleepiness was similar between modafinil treatment groups and placebo. These are much smaller studies Additionally, the observed incidence was lower compared to ADHD pediatric studies. Only one event was reported as severe for events described by the investigator as fifth disease. No events led to discontinuation or were serious by regulatory definition.

[Slide]

The observed imbalance in incidence of

non-urticarial rash in the controlled ADHD pediatric studies prompted further evaluation for possible association with treatment. We approached this in 3 ways. We evaluated the relationship between rash and dose; relationship between rash and modafinil plasma exposure; and, finally, we evaluated the relationship between rash and modafinil sulfone exposure, one of the metabolites known to be present in higher concentrations in children. With respect to relationship of non-urticarial rash and dose, we conducted a case-control analysis where patients with rash were matched with controls based on the study protocol, time in the study to event and weight. Based on this analysis, we did not find statistical evidence for association between rash and modafinil dose.

[Slide]

A second analysis looked at the modafinil plasma exposure by comparing area under the curve between patients reporting non-urticarial rash, in the far left box on the slide, controls, in the middle box, and overall patient population in Phase

3 studies, in the far right box. Areas under the curve were calculated based on sparse sampling data from the Phase 3 trials and PK modeling. As presented on this slide, no difference was apparent between the 3 groups.

[Slide]

An assessment of the relationship between non-urticarial rash and exposure to modafinil sulfone was also conducted. Here we graphically depict the distribution of modafinil sulfone concentrations in patients developing rash--small red boxes at the bottom, and in patients not developing rash--blue boxes. On the Y axis the number of patients is depicted and different modafinil sulfone concentration ranges are depicted on the X axis.

We observed that the distribution of sulfone concentrations in patients with rash appears to closely mimic the distribution of sulfone concentrations in the full population of treated patients in placebo-controlled studies. We conclude, therefore, that there appears to be no

correlation between non-urticarial rashes and systemic exposure to modafinil sulfone. One additional piece of information is that 2 cases in question had modafinil sulfone concentration of less than 6 mcg/ml.

[Slide]

We have also examined the adverse events database from the controlled ADHD pediatric studies for COSTART preferred terms indicative of urticaria, hypersensitivity reactions or allergies. This slide presents a tabular summary of the reviewed preferred terms and associated medical history reported prior to treatment initiation. One can easily see from the table that the vast majority of these events was reported in patients with prior history of seasonal allergies or asthma.

[Slide]

Psychiatric adverse events related to ADHD treatment have enjoyed special interest in the recent months, culminating in some important discussions as recently as yesterday. In response to the request from the Division issued to all ADHD

drug manufacturers, Cephalon has performed a full analysis of psychiatric events from all pediatric studies and from our pharmacovigilance database as per prespecified methodology.

In addition, we have reviewed serious adverse events occurring after the last safety update cutoff in October, 2005, covering the period through February 1, 2006. The results will be presented in the next several slides.

DR. GOODMAN: Excuse me just a moment, I want to ask a question of clarification on the previous metabolite levels that you showed. What was the relationship between the timing of obtaining the sulfone metabolite level and the dosing? Obviously, there can be a lot of noise contributed by relationship between time of assay and dose.

DR. STANKOVIC: We obtained the values for concentrations of modafinil sulfone closest to the event for those patients that reported a rash.

DR. GOODMAN: But it might not have been the same relationship to the time the dose was

actually taken. Right?

DR. STANKOVIC: That is right, yes. That is correct.

[Slide]

A brief introduction on methodology of the psychiatric evaluation, all adverse events reported in the ADHD and excessive sleepiness pediatric programs were subject to a review by a string search for COSTART preferred terms of investigator verbatim terms indicative of psychiatric events. Once identified, all events are classified in the following groups, psychotic events including mania, suicidal ideation and behavior, aggressive and violent behavior and miscellaneous psychiatric events that were serious by regulatory definition. A similar string search approach was employed in the review of our psychovigilance reports. Event terms and narratives from the ongoing pediatric studies for serious adverse events were reviewed in order to identify psychiatric events as well.

[Slide]

We present here psychiatric adverse events

from the ADHD pediatric program. Just a quick note, this table includes both events that occurred during treatment as well as those that occurred 48 hours following last dose of modafinil. As I will be discussing these cases, we put them together. This is somewhat different than the methodology applied in the tabulations presented yesterday.

In the controlled studies all psychotic events, as well as all events of suicidal ideation or behavior were reported in modafinil treatment groups. Reports of aggression or violent behavior were relatively balanced between treatment groups, with a slight higher proportion of these events occurring in placebo. Additionally, no serious miscellaneous events were reported in either group. When the smaller pediatric program in excessive sleepiness was examined, no psychotic or suicidal events were found. Obviously, even few events or a psychotic or suicidal nature are a great concern so we will review them in more detail.

[Slide]

A total of 5 patients reported psychotic

symptoms while on modafinil treatment, all within 48 hours post last dose. Three of these events were relatively short in duration and why patients continued modafinil in one case or following withdrawal of the drug in two cases. One additional case, described as psychotic disorder aggravated, was also relatively short in duration but did require hospitalization and led to withdrawal from study. This case, also in the narrative, we learned reported as suicidal verbalization but it is included in this table in the psychotic disorders. The fifth case was an interesting case of reported ideas of reference that apparently did not require any specific treatment--yes, sir?

DR. GOODMAN: We have a question.

DR. PINE: I want to understand both of these cases because the last two cases don't really make sense to me and I am wondering if you could go into them in a little detail, really the last case more than the second to the last one. When it says psychotic disorder aggravated, that implies to me

that there was either a preexisting psychotic disorder or some other factor that was contributing and it sounds concerning that the child was hospitalized. So, that is one question.

The second question is that this is a case of ideas of referential control which, again, sounds somewhat concerning and the event lasted ten months, which is also somewhat concerning if those are really ideas of referential control, but the action taken was to continue with modafinil. So, that doesn't make any sense to me. I wondered if you could explain those situations.

DR. STANKOVIC: Yes, I can talk a bit about those cases additionally. The psychotic disorder aggravated is an 8 year-old boy with ADHD. He presented with severe psychosis beginning on day 19 of the open-label study. He was hospitalized and at the time of hospitalization we learned that there was a prior history of a psychotic disorder that was not reported at the time of the entry to the study.

The second case is a very interesting case

to us as well. Unfortunately, we do not have quite a clarification of continuing modafinil treatment in ten months of continued ideas of reference. We don't have any additional details. It is interesting and somewhat confusing but that is what happened. The investigator continued treatment for an additional ten months.

DR. PINE: Just to make a comment about that, I mean, not only does that raise questions about this case but it raises questions about the nature of the data in general because it just wouldn't make sense that somebody would see something like this, and idea of reference, that would be ongoing for ten months but not feel the need to take any treatment. Anyway, I guess it speaks for itself.

[Slide]

DR. STANKOVIC: We have here a similar presentation for the 5 patients reporting adverse events classified as suicidal ideation or behavior. The first 3 patients experienced brief episodes of suicidal ideation, described as suicidal statement.

In 1 patient this happened on 2 occasions. None of these events required either treatment for the event or study drug discontinuation. One patient verbalized a suicidal threat which was resolved after study drug was discontinued.

One case, however, is a case of aggressive behavior reported initially as normal behavior. The case narrative described suicidal behavior in a 6 year-old girl with a psychiatric history and possible family history. The event occurred 2 days following the last dose of study medication and required hospitalization and prolonged treatment.

[Slide]

Between the last safety update in November, 2005 and February, 2006 4 serious adverse events indicative of suicidality of psychotic symptoms were reported in the ongoing pediatric studies. These include both ADHD studies and ongoing pediatric studies in excessive sleepiness. Three patients reported events that were classified as suicidal events, ideation or gesture. In 2 of these cases no treatment intervention was required

and the patients continued in the study. Treatment was withdrawn for 1 patient. One additional patient reported paranoid reaction following 16 days of treatment. The event lasted 5 days and the study drug was withdrawn.

[Slide]

In the request from the Division for analysis of psychiatric adverse events, we have been asked to review postmarketing reports received during the period January, 2000 to June, 2005. We estimate that for this particular period the total pediatric exposure approximates 24,700 patient-treatment years. A total of 7 psychiatric reports were received during this period.

[Slide]

These are the events reported. The events were reported in a wide ranges of ages, as you can see, from 6 to 17 years, and across both genders. Four events involved psychotic symptoms. One event was reported as a suicide attempt. However, in this case modafinil was not taken prior to the event but was only taken as a part of the cocktail

of drugs used in the multi-drug overdose. The 2 remaining cases are events of aggressive symptoms and violent behavior.

[Slide]

You may wonder at this time how does the safety profile of modafinil observed in pediatric ADHD studies compare to other programs in children. We have one additional program, smaller, completed as a part of the pediatric retail request in narcolepsy and obstructive sleep apnea for excessive sleepiness. I will review here the general safety profile observed during the pediatric development program in this indication.

[Slide]

Overall, a similar safety profile was observed in the small patient population; a similar AE profile, effects in vital signs or laboratory parameters were observed. Notably, no adverse effects on weight were observed during the short-term trials in this patient population. Lower incidence of non-urticarial rash was observed compared to ADHD studies, and no events led to

discontinuation or were serious in nature.

[Slide]

One serious adverse event from the pediatric studies in excessive sleepiness requires discussion as it was mentioned as a point of concern in the FDA clinical review as a possible case of Reye's syndrome.

The clinical picture in a 6 year-old boy was that of a non-specific viral syndrome--nausea, vomiting, pharyngitis, followed 3-4 days later by a change in mental status characterized by somnolence, delirium, hallucinations and seizures. The patient had elevated serum ammonia but not transaminases.

The case was reviewed at Cephalon's request by two external consultants, one pediatric neurologist and one pediatrician. The consensus opinion was that the most likely diagnosis was viral encephalitis or inborn error of metabolism. Urea cycle disorder was mentioned. Reye's syndrome was considered unlikely because of normal LFTs. According to the FDA briefing package, the FDA

consultant also concluded that this case is not drug related.

[Slide]

Some of the postmarketing information has been reviewed earlier as part of the discussion on skin and psychiatric reactions. Here we will review the profile of the reported events through our pharmacovigilance system from the perspective of different system organ classes.

[Slide]

First, review of estimated postmarketing exposure, we estimate that as of February, 2006 total postmarketing exposure to modafinil was 780,000 patient-treatment years. This includes worldwide exposure for the period since drug approval in the first country in 1999. As it appears, based on the prescription data market research that we have, 4 percent of these exposures included individuals less than 18 years of age so we estimate that the overall pediatric exposure is about 30,000 patient-years. Based on some information that we have available, the estimated

median duration of treatment with Provigil in the market is approximately 3 months. So, using those numbers, one can estimate exposure to modafinil to be higher than a million, up to 3 million adults and in excess of 100,000 children.

[Slide]

Presented on this graph are comparative profiles of postmarketing adverse drug reactions reported for adult patients, in blue rectangles, and pediatric patients, in orange. The total number of reported adverse drug reactions in a particular system organ class is presented on the Y axis while different system organ classes are presented on the X axis. We had a total of 105 adverse drug reaction reports for all pediatric patients.

As you can see, although it is a little hard on this slide, the two profiles appear largely similar across different organ systems. It should be noted, however, that the we do not have reliable information on how the two populations relate with respect to underlying indications for which the

drug is prescribed or doses used.

[Slide]

Based on the postmarketing reports, the Provigil label is continuously reviewed and updated as deemed necessary. This slide is a reminder of 3 label changes initiated by Cephalon within the past 3 years. As you can see, some of the safety events observed in the pediatric ADHD program are fairly consistent with the postmarketing experience that resulted in label changes.

[Slide]

I have reviewed a considerable amount of safety information and will try in the next two slides to briefly summarize the main points. We believe that it is fair to say that modafinil is generally well tolerated at doses studied. Not unusual for ADHD medication, the most frequently reported adverse events were insomnia, headache and anorexia. These events were seldom severe and few led to treatment discontinuation. Likewise, few significant laboratory abnormalities were observed. No effects on mean systolic blood pressure,

diastolic blood pressure, pulse or QTc interval were observed in the controlled trials.

[Slide]

Beyond initial weight loss, there were no consistent adverse effects on growth observed over 12-month treatment with modafinil. We did observe events of suicidal ideation and psychotic events in the ADHD pediatric patients treated with modafinil. These events were short in duration in general and did not require additional treatment in many cases. We believe that there is one case of probable Stevens-Johnson syndrome reported in the pediatric clinical program so far at this point, at an exposure of 1622 patients. This case resolved without any adverse sequelae. As I mentioned, I am sure that there will be more discussion of this case and we will hear from the investigator and consultants on this.

[Slide]

In the next presentation Dr. Lesley Russell will review--

DR. GOODMAN: Before you go to that

presentation, Dr. Rappley?

DR. RAPPLEY: I have two questions; the first, in the 30,000 children that you expect were exposed in the postmarketing period, do you expect that most of them received the 200 mg dose?

DR. STANKOVIC: As I said, it is very difficult to know exactly what dose was prescribed and for what indication it was prescribed so I cannot comment on that. I don't really know. As Dr. Temple mentioned earlier, one can assume a variety of things. Whether it was 200 mg or higher, we don't know.

DR. RAPPLEY: And, in your study 310 it was cited for not obtaining hematologic values, and one of the sites was with 21 patients. In looking at your table on slide 76 which describes neutrophilia, to what extent did those missed samples affect your data? How many samples were missed?

DR. STANKOVIC: I can't give you the exact number; I don't know it off the top of my head, but I think that the number of analytes may be 390 or

maybe 20 or 30 patients that don't have all of the analytes, but I am not positive about that. I can find you that number.

DR. RAPPLEY: Thank you.

DR. GOODMAN: Dr. Leon?

DR. LEON: I would like clarification on the case control analysis you did. In the sponsor book it is on page 64-65. You very briefly made reference to your analyses--

DR. STANKOVIC: Yes.

DR. LEON: --in your slides, that you found no risk of a variety of dosing factors for the rash. It was a dependent variable. It was a case control where you had 39 cases and 3 times that number, 117, controls apparently matched on 3 variables. I have some questions.

First of all, it looks like you entered about 14 variables that were very highly correlated simultaneously. I mean, that is what it says here. The effects were measures of dose entered at one time.

DR. RAPPLEY: Will you show us the

document you are referring to? Is it this one?

DR. LEON: Yes. Sponsor's book page 64-65. I mean, this is being used as evidence of no association when the analyses were not conducted in the way that I believe an association would be detected. So, my first question has to do with entering all those variables simultaneously, very highly correlated measures of dosing.

My second question has to do with what is the statistical power you would have with this sample size? You would have statistical power to detect what effect? The sample size is only 39 versus 117. Would that be an odds ratio of maybe 2 or 2.5? You could miss some pretty substantial associations.

Third, did the analyses account for the clustering of these sets of 4 who were matched? In what way did it account for it?

DR. KINGSBURY: Let me address these one at a time. First of all, let me inform you that we did not use all 14 variables at a time. This was just different approaches to explore those and they

were done one at a time. Okay?

First of all, let me describe the matched control analysis that we did. There were 39 cases. We found 3 matched controls, as described in the briefing document. As already indicated they were matched by the study they came from; by the weight stratum they were in; and also by having been in the study at least as long as the time taken for the event to take place. So, in that set, using each of those 14 variables one at a time, we looked at the distribution of whatever the dose was in quartiles and tried to ascertain whether there was a relationship, but understanding the limited power. This is more of an exploratory analysis--

DR. LEON: What was the way that you accounted for the clustering of these quartets of case controls there? What was the analysis?

DR. KINGSBURY: I am sorry?

DR. LEON: Well, you have groups of people, as you would in a paired T-test if you had diads, and you have sets of 4 people who are matched on these criteria that you just described,

and I want to know what is the statistical analysis that was used to account for this clustering, the correlation among these sets, these quartets.

DR. KINGSBURY: We did essentially a conditional logistic regression in which we defined this stratum as the case. We identified each case and the corresponding matched controls. Then we looked at the odds ratios of each of the various increasing quartiles relative to the fist quartile just to get a sense--I mean, this was very much a descriptive statistical approach to see if there was any evidence of a consistent dose response. We did not find that.

DR. LEON: So, you acknowledge limited power. You have power here with 150 subjects total to detect what size odds ratio? Just so you can let us know the magnitude that might have been missed there.

DR. KINGSBURY: Because it was not an a priori designed analysis, we did not focus on that issue. We actually did not test anything; we were just obtaining confidence intervals because that is

all we felt would be appropriate. As I mentioned before, although the confidence intervals overlapped 1, the odds ratios extended from 0.09 to a little over 2.

DR. LEON: But when you are looking to see if confidence intervals are overlapping 1, then you are doing tests, exactly the same as looking at p values. You are getting more information as well about the magnitude of the change and about the variability of that change, that association.

DR. KINGSBURY: We don't claim to have shown no association. All the conclusion we are making is that--by the way, consistent with the limitation in the numbers that we have no compelling evidence of an association, we did an additional analysis based on the randomized clinical trial data, and from that analysis we found an odds ratio of 1.4 with a confidence interval extending from 0.678 to 3.094. Going back to the case control analysis--

DR. GOODMAN: Thank you very much. Let's go on to our next speaker. Thank you.

[Slide]

DR. STANKOVIC: The next speaker is Dr. Lesley Russell.

Benefit-Risk Conclusions

DR. RUSSELL: Thank you, Dr. Stankovic. We have presented a lot of information this morning regarding the efficacy and safety profile of modafinil in the treatment of ADHD.

[Slide]

Following your deliberations, you will be asked to answer two questions, the first being has modafinil been shown to be effective for the treatment of ADHD in children and adolescents?

We believe that the answer to this first question is yes. In the 3 pivotal studies consistent benefit of treatment with modafinil was seen in all 3 studies, with these effects observed by the teacher, the parent and the treating physician across different rating scales and instruments, and with effects being observed both at home and at school.

[Slide]

You are also going to be asked today whether modafinil has been shown to be acceptably safe for the treatment of ADHD in children and adolescents.

In the Phase 3 clinical program modafinil was generally well tolerated. The most common adverse events reported, insomnia and anorexia, were generally mild to moderate in severity and rarely a cause for treatment discontinuation. No adverse signals were observed in the Phase 3 program with respect to pulse, blood pressure or growth.

We were asked in the approvable letter to provide more information on 3 cases of liver transaminase elevations. As outlined in our response to the approvable letter and presented here today, in 2 of these cases the transaminase elevations were resolving on continued treatment with modafinil with, in 1 case, ALT values returning to normal whilst continuing treatment. In the third case the transaminase levels were returning to normal on discontinuation of

treatment. We do not believe that an adverse signal with respect to liver function has been observed.

Concerns have been raised over the reporting of psychiatric adverse events. As you are aware, these events were fully discussed yesterday at the Pediatric Advisory Committee for all ADHD products. Although no consensus was reached on how to label aggression, psychosis, mania and suicidality, Cephalon has proposed language in the warning section of the label which we believe provides appropriate information regarding these events seen in our clinical program.

[Slide]

Concerns have also been raised over the reporting of serious skin reactions, and in the approvable letter we were asked to provide you with more information on 3 cases of interest seen in the clinical trials and 4 cases reported in adults in the postmarketing setting.

As suggested by FDA, these cases were

reviewed by experts in the field and there appeared to be general concurrence reached by these reviews and Dr. Porres, from the FDA, with respect to the first case, the 7 year-old boy with possible SJS. But there does appear to be some diversity of opinion regarding the other 2 clinical trial cases. This seems to be in keeping with the diagnostic and etiologic uncertainty surrounding the diagnosis of these types of skin reactions. However, we acknowledge that an association with modafinil cannot fully be excluded. In all 3 of these cases, however, the events did abate following discontinuation of drug and no adverse sequelae occurred.

In assessing the risk for SJS and reviewing the totality of the data in the clinical trials and postmarketing database for both adults and children as reviewed, we believe that the risk for SJS is low. However, we have proposed language to be included in the warning section of the label. Based on your deliberations today, we will be happy to modify this as appropriate in order to provide

patients and healthcare providers with adequate information concerning these events.

Lastly, modafinil is not a new chemical entity and to date there have been 780,000 patient-years of exposure which, when looking at actual patients exposed, may equate to approximately 3 million exposures since introduction of the drug in France, in 1994.

Pharmacovigilance is undertaken to assess risks associated with modafinil usage and, as you have heard today, this has led to 3 labeling changes, one regarding the incidence of severe skin reactions. Cephalon is committed to improving these risk assessments further by undertaking a more structured case ascertainment with respect to skin adverse events.

[Slide]

So, in conclusion, we believe we have shown you today that modafinil is an effective treatment for ADHD with an acceptable safety profile, with the benefits of treatment outweighing its risks. Thank you for your attention.

Questions from the Committee to FDA and Sponsor

DR. GOODMAN: Thank you. May I suggest that your team stay at the podium to address some questions? I am going to assume that most of the committee members are going to have questions for you. If we start to run out of time, we are going to have more opportunity to ask those questions later this afternoon.

Let me start off with what may be the easier of the two questions we are asked to vote on today, the one regarding efficacy. From the FDA standpoint and what I read, they were satisfied with the efficacy data. I certainly feel satisfied from what I have seen. Yet, before we move on to the harder question of evaluating issues of safety, it is very important to have the context in mind of the benefit.

So, I want to give you an opportunity to answer, from your perspective, where you see this medication fitting in; where is it going to add value or options in the marketplace? Is it going to be advantages in the area of efficacy,

tolerability? I wonder if you could just expand on those issues to give a little bit of a framework to think about the benefits of this medication.

DR. RUSSELL: Well, as you heard from Dr. Biederman with the MTS study, despite treatment with drugs that are considered to be very effective--and we certainly don't doubt that--there does remain a group of patients that still either cannot tolerate drugs or don't respond to them. We saw in our program that, although maybe not considered refractory, patients who had failed on a prior stimulant therapy did appear to benefit from the drug. We also saw that if you are stimulant naive you respond slightly better to the drug.

So, we see this as a viable treatment alternative to other drugs that are obviously commonly used and considered to be effective agents. However, I would like to have a treating physician in the field come up and maybe give you that from his perspective. So, if I could ask Dr. Biederman?

DR. GOODMAN: Sure, go ahead.

DR. BIEDERMAN: I think that in clinical practice we need alternative treatments to treat our patients. The idea that the most efficacious treatment treats all our patients is not true to life. So, clinicians in practice need to have options to allow us to better serve the people that consult with us.

The issue of adverse effects is a statistical issue. That means that even if side effects are similar within a class of drugs, some patients clearly tolerate one versus another even if on average they have a similar spectrum of adverse effects. So, patients that have poor tolerability may benefit from a drug that may have on average similar issues but may be better tolerated for them.

Finally, the issue of scheduling--I think that even though many of the new generation stimulants that are available today are clearly less of an issue for diversion and abuse, many clinicians and many families do not want their children to be on a Schedule II drug. So, I think

that this gives an option for clinicians to use a lesser scheduled drug in cases where they choose not to use a scheduled compound.

DR. GOODMAN: Joe, before you step down, has it been your impression so far that there is less abuse potential, less potential for diversion as, say, compared to stimulants?

DR. BIEDERMAN: Yes. I am not an expert on abuse and we have here a colleague that specializes in that. The abuse and diversion--first of all, let me comment on abuse and diversion. There are different publics that use these drugs recreationally and therapeutically. Our battles in clinical practice are to encourage our patients to remain in treatment. There is a very severe problem of non-adherence to these treatments. So, it is not something that our patients look forward to taking.

The attraction of the stimulants is when the tablet can be crushed and snorted for an IV-like experience. It is the parenteral intake that produces the euphoria, not the oral intake.

So, this drug is not snortable, injectable, and so on and so forth, so it is not a drug that the addict community on the street would pay a high price for to get it. But maybe we can get some of our colleagues that are here with better expertise than mine on diversion and abuse to give a perspective.

DR. RUSSELL: Does that answer your question?

DR. GOODMAN: I would like to hear a little more on that issue.

DR. RUSSELL: Dr. Dackis?

DR. DACKIS: With regard to the abuse potential of modafinil, I think it is important to note that it is chemically unrelated to central stimulants and has a very weak effect on the dopamine transporter so that it is extremely unlikely to increase dopamine levels, except in very high dosages.

There have also been a number of studies in humans to assess what the subjective effects of this agent are and these studies, which have been

conducted by Jasinski demonstrate that in males there is no effect of modafinil. There was a smaller study in females that did show some stimulant effects using these various rating scales. Two other studies, again, showed that there was not a significant high; that the subjects were not willing to pay money for modafinil, etc.

In addition, animal studies, looking at things like self-administration and condition-place preference showed very weak stimulant-like effect of this agent. So, there is some reinforcing quality but it is very, very weak. DR. GOODMAN: I thought monkey studies showed preference.

DR. DACKIS: Yes, that is correct. Gold and Balster's study did show that monkeys, trained to self-administer cocaine, if given modafinil would continue to self-administer large doses of this agent, as they would with other compounds like ephedrine. So, large doses are required to continue to self-administer.

DR. GOODMAN: Thank you. Dr. Temple?

DR. TEMPLE: I am sympathetic to the idea

that drugs with different pharmacology may have different usefulness, but I want to address the question of whether they have documented the ability of this drug to work in people who are resistant to stimulant drugs, and the answer is that they have not.

There is a perfectly simple, never done kind of study design to do that. You take people who fail on whatever it is you want to test and then you randomize back to that drug and to the new drug. It is a perfectly simple study. That is how clozapine came to the market because we wouldn't have approved clozapine unless it worked in failures because of the 1.5 percent agranulocytosis. That study could be done. You might even think about whether it is something that ought to be done, but it has not been done. The mere fact that people given a second drug after failing the first respond to it tells you nothing at all. We have many examples where drugs don't particularly work in non-responders to other therapy but the second time around the people do

better. So, I just want to make it clear they have not shown that. It might be true. It is plausible even but it hasn't been shown.

DR. PINE: Can I ask a question about that? Of course, there have been other medications that have been discussed over the last couple of years for new indications for ADHD and I am sure that that issue came up. I think that those studies have not been done and what was the thinking and discussion around that?

DR. TEMPLE: Well, they are almost never done. We don't usually have a reason to say, for example, only use this drug in people who have failed on other therapy, if one thought that was an appropriate thing because I am not saying you should or not--you are going to get to that. I am just making the point that they have not documented in a rigorous way that the drug would actually work in those people. You might think that there is a little evidence that it does, and you might think the pharmacology difference suggests that it might, all of which I agree with but that hasn't been

studied and it can be studied, and it never is studied.

DR. PINE: For what it is worth, my take on it would be that that would only be one of the potential uses of the medicine clinically, and it seems like some of the other issues are, you know, kind of bigger in terms of thinking about the medicine as opposed to, you know, is it primarily for people who don't respond to stimulants.

DR. REESE: We are going to get to everyone's questions. First we are going to have Dr. Bronstein and then we will have Dr. Wang. Thank you.

MS. BRONSTEIN: My question is a fairly straightforward, easy one. On slide 93, in the Phase 3 study you have one person who had a severe event and withdrew from the study. What kind of rash was this?

DR. RUSSELL: Unfortunately, the only description on the case report form, which reflects the source documents, is just a verbatim of rash so I am unable to describe it further for you.

MS. BRONSTEIN: We can assume though that it was severe.

DR. RUSSELL: It certainly led to discontinuation of the drug. That is all the information I can give you.

MS. BRONSTEIN: Thank you.

DR. REESE: Ms. Dokken?

MS. DOKKEN: Yes, I apologize, I thought we were supposed to hold our questions until the end so my question really goes back to slides 30 and 31 and this issue of the 40 percent who are non-responders or had intolerable side effects. I am wondering whether anyone can sort of unpack, you know, how many people are in which category because it seems to me that what we have been hearing is that one of the marketing messages for modafinil will be that it is an alternative. If it is an alternative and we are talking about whatever percentage of that 40 percent are ones who suffered "intolerable" side effects, certainly this particular drug--and those of us who were fortunate or unfortunate enough to be present yesterday, you

know, the side effects are present in almost all. Then that leads me to the worry about the next step which is, you know, if it were approved how is it marketed and what are the messages because probably it was the Pediatric Advisory Committee that has seen, you know, other situations where something is marketed as being free of something else, suggesting that there are no risks and to say that because it is a non-stimulant it has no risk would be a concern for me.

DR. TEMPLE: Drug advertising reports to me so I have to worry about this. We are fairly careful about making claims when you don't have a direct comparison and there aren't any direct comparisons. However, if one is scheduled at a different place, or something like that, that is true and they would be allowed to claim that.

There are some cases in which the difference in certain side effects is so obvious--like it never happens with this and it happens all the time--where we might allow something like that. But we are very careful about

comparisons in the absence of actual comparative data across study comparisons and treat it with suspicion.

DR. REESE: Dr. Pfeffer?

DR. PFEFFER: Thank you. I am not questioning the efficacy but I have some questions on slides 52, 53 and 54, please. Maybe you can help us understand the longitudinal process of the three studies. For example, it looks as if in slide 52 I guess efficacy was being demonstrated by week 5. Then in slide 53 and 54 it seems that it was earlier, although on slide 53 at week 5 there was perhaps less of that. I don't know if that is due to dropouts and then resumption.

So, my question is on the early phase of these, week 3 and even week 2 on slide 54, what were the general doses that the children were on at that point in time? Then, if you can tell us what happened in week 5, on slide 53? Finally, if you could tell us a little bit about when were blood tests taken in the process of the study and when did the side effects emerge, especially skin

reactions, etc.? I am trying to link the time course with the doses and the longitudinal course.

DR. RUSSELL: In study 10, which is the slide up here, this is the fixed dose study so that by the second week patients would have been titrated to that target dose. That would have occurred by day 7 for those randomized to 340 and day 9 respectively.

DR. PFEFFER: I thought I understood that but my concern is if, in slide 53 and 54, you see earlier efficacy is that at the target dose or less than the target dose?

DR. RUSSELL: In this study, which is the fixed dose study, they would have been at target dose.

Could you go back to the previous slide for 311, please? This is one of the flexible dose titration studies. So, in the earlier weeks they would have still been titrating up.

DR. PFEFFER: Do you know approximately the average doses at the early phase?

DR. RUSSELL: Probably around 255 mg by

the second week and up to the 340 mg by the fourth week.

DR. PFEFFER: And on slide 54 it is similar. Is that right?

DR. RUSSELL: Slide 54, which I think is study 310, is where they titrated up more quickly so they would have been at target dose by day 7 and 9 respectively.

DR. REESE: Dr. Armenteros and then Dr. Malone?

DR. ARMENTEROS: Just to follow-up a little bit on the dosing question, I understand the model that you used to dose the two groups of children, you know, below 30 kg and above. Now, most of the children that got into the study were above 30 kg, like 68 percent that you mention here. Now, when you presented data on efficacy there wasn't a differential response between these two groups by weight.

The reason that I ask that question is that we already know from your previous studies that at lower doses you do get response for daytime

sleepiness, and so forth. So, I don't know if we may be missing perhaps different points in dosing at which these kids may respond. Because at the end of the trial I come out with a very fuzzy impression of what the actual dosing should be and I hope I can get a better understanding.

DR. RUSSELL: First let me answer the excessive sleepiness programs first because what we do find is a very different pharmacodynamic response when we are treating excessive sleepiness than when we are treating ADHD. So, in the excessive sleepiness programs and the pediatric narcolepsy, although we looked at doses of 100 mg through 400 mg, doses of 400 mg were clearly efficacious in that model. Then we did some PK/PD work and the target exposure needed for an effect in narcolepsy is substantially lower than the target plasma exposure associated with effect in ADHD--so very different pharmacodynamic response which I don't think I can explain, but it is very different.

In terms of looking at the doses and how

did they respond to efficacy, what we did was to look at the different quartiles of dosing and in the third and fourth dosing quartiles, which are the higher dose groups, you see numerically a slightly higher response but it is only a point or two. So, I would say that the dose response, with all the caveats because we were titrating to a target dose, is flat in the doses that we looked at here.

DR. REESE: Dr. Malone?

DR. MALONE: I have two questions. One is on efficacy. The stimulants wear off every day by the end of the day. Is that true for this drug? I am just wondering if it is like the stimulants, that you have to dose it every day; you dose it in the morning and then it wears off by the evening.

DR. RUSSELL: The only data we have with respect to that is actually in the 2-week withdrawal period where the patients who had received modafinil during the double-blind treatment period were randomized to either stay on modafinil or were randomized to receive placebo.

What we see is not an immediate return to baseline in symptoms but a more gradual return towards baseline and their symptoms. So, based on the limitations of that data which I acknowledge here, there doesn't appear to be a sort of complete rebound effect.

DR. REESE: Dr. Bigby?

DR. BIGBY: I have a question about the ADHD rating scale. If you gave this test to a group of normal kids who don't have ADHD, what would their score be?

DR. RUSSELL: The average for a 10 year-old boy I think is 18.8, and the children going into our study had an average of around 37. So, they were clearly much higher than what would be considered to be normative for a 10 year-old boy, which was the average population in our study. It does differ a little bit based on whether you are a boy or a girl or your age, but that appears to be the average for a 10 year-old boy.

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: In one of the studies you

actually did a withdrawal phase but I believe the data weren't shown.

DR. RUSSELL: That is right.

DR. TEMPLE: You must have a slide of it. That would answer the question of how soon it wears off.

DR. RUSSELL: If I could have the slide, please?

[Slide]

This is over the 2-week withdrawal period. You can see on the right-hand side that the placebo at the end of the 7-week period and the end of the 9-week period obviously stays the same. In the modafinil group there is a point difference, but for those who were on modafinil and then got changed to placebo you can see that there is a beginning of deterioration of their symptoms over that 2-week period. It is not huge but there is a deterioration and it looks like they are returning towards baseline. But there doesn't appear to be a sort of instantaneous effect.

DR. TEMPLE: And you don't have it day by

day or anything like that?

DR. RUSSELL: Unfortunately, we don't.

DR. REESE: Dr. Malone, your second question and then Dr. Rappley.

DR. MALONE: It was really I guess partly answered. It had to do with the abuse potential for modafinil. I think, from the reading, it did say that it can cause euphoria and that animals would work for this drug. If that is true, I just have a question why would a stimulant be a Class II and this a Class IV? How do they decide that?

DR. GOODMAN: Dr. Temple or Dr. Laughren? I have a very similar question about the classification. Currently this drug is classified Schedule IV compared to the stimulants which are Schedule II. Could you just explain that distinction? It would be in the context of a quick follow-up I was going to do and ask sponsor how they would best characterize or classify their compound.

DR. LAUGHREN: Actually, FDA doesn't decide that classification. The decision is made

by the Drug Enforcement Administration. They do an 8-factor analysis. I haven't looked at that. Maybe the company could respond to, you know, how it is that the DEA arrived at a Class IV rather than a Class II.

DR. TEMPLE: There is a very sharp distinction between the level of control. I think we are about to hear about that. II is, you know, locked cabinets and all the rest; IV is much less.

DR. GOODMAN: Yes, please, could we hear about that?

DR. RUSSELL: The difference between a Schedule II and a Schedule IV, is that what you are asking?

DR. LAUGHREN: How it got a Schedule IV rather than a Schedule II.

DR. RUSSELL: I wasn't with the organization at the time of the original scheduling. Perhaps I could ask Dr. Vaught, who was here, to explain how that happened.

DR. VAUGHT: Good morning. My name is Dr. Jeff Vaught, executive vice president for research

and development for Cephalon.

[Slide]

I would like to very briefly just go over the aspects of scheduling which, certainly the agency knows as well as I do, has to do not only with the physical chemical characteristics of the compound but also testing that is done in human beings to suggest that there is a reinforcing property. So, if we look at the overall physical chemical activity of modafinil, it has very, very low water solubility which is incompatible with intravenous injection. It is very unstable at high temperature, therefore, it is incompatible with smoking. Importantly, it is structurally unrelated to other agents that are known to be abused. While it does have a very, very weak--and it is really the only neurochemical effect that we have been able to demonstrate in blood receptor binding assays, etc.--with dopamine. It doesn't appear to cause elevations of dopamine of nucleus accumbens, which is markedly related to drugs of abuse, as well, it has not releasing properties as do other

Schedule II stimulants. There is also lack of activation, as I mentioned, of reward centers, and really the results, as Dr. Dackis described to you, from preclinical studies suggest that if there is a signal it is very, very weak.

Now, all this is theoretical because that is all nonclinical data. Perhaps more importantly and something that we undertook at Cephalon spontaneously, is a postmarketing surveillance, starting in 1999 with the Haight Ashbury group. The Haight Ashbury group monitors a variety of areas worldwide where drugs may be diverted to, including rave scenes, medical professionals, etc. Now that we have had six years we still have reporting on this. There have been limited to no reports of euphoric effects. There are no reports of reinforcing effects. There has been a very large increase since the drug has been approved for wakefulness for mainstream publicity regarding the use of modafinil, including in The New Yorker magazine, college newspapers, etc., and across the Internet every now and then we will see postings of

potential use but nothing that is consistent. In fact, the Haight Ashbury concludes after evaluating this for the last six or seven years that if there is abuse potential for modafinil at all, it is very, very low.

So, all of this is consistent with what is seen as an agent with low abuse potential. We now have considerably more experience with the substance than we did five or six years ago when we were getting approval and we thought that was consistent with the regulatory standards for Schedule IV.

DR. GOODMAN: Thank you. Apart from how DEA will classify your drug, how would you internally classify it? Would you say it is a stimulant or is it distinct based upon its mechanism of action, which I understand is unknown. Although I know at one time it was thought to be mediated through orexin receptors, I guess that is not as firmly established at this point.

The reason I ask is not just a semantic question but whether it gets counted or considered

a stimulant may have labeling implications. As revealed by discussions yesterday, for example, Strattera, should that be considered a stimulant and, if so, should it have certain warnings attached to it that go with the rest of the class of stimulants? So, I would just like the sponsor's perspective on whether you would classify this medication as a stimulant or not.

DR. VAUGHT: We approach this from a couple of levels. One is the preclinical data that we have, as well as the clinical information. In direct answer to your question, I would not classify it as a traditional sympathomimetic stimulant. It is a CNS activating agent and we have all been taught, prior to the introduction of modafinil, that, in fact, most of our CNS activators are psychostimulants. Nonclinically, modafinil has a profile of wake-promoting activity that, unlike the classical stimulants--its wake-promoting activities are not blocked by haloperidol which has been characteristic of wake, if you will.

As far as the orexin component that is involved, we have been able to demonstrate it has no interaction with the orexin system because in knock-out animals, as well as human beings and dogs it is highly effective. When we move to human beings, we similarly don't see the typical types of profile that one sees with the stimulant population. If we include this with methylphenidate and amphetamines this includes sympathomimetic-like effects as well as generalized excitation reinforcing properties, euphoric effects, etc. So, overall the pharmacology would suggest that if we want to classify it as CNS activating agent it is certainly a non-traditional agent.

DR. GOODMAN: Would you say that it has less peripheral--if you look at the relationship between CNS, there is relatively more CNS to peripheral activation?

DR. VAUGHT: Yes.

DR. GOODMAN: That was my last question.

DR. REESE: Dr. Rappley?

DR. RAPPLEY: My question goes back to the safety area and pharmacodynamics. Dr. Mannheim noted that we don't have information about steady state for the sulfone metabolite. We know it accumulates to a much greater extent in children but we don't know quite when that steady state is achieved and I wonder if you have more information about that.

DR. RUSSELL: The sulfone metabolite appears to reach steady state at about 2 weeks and then it actually plateaus thereafter.

DR. REESE: Dr. Wang?

DR. WANG: I have one more housekeeping question about efficacy. Are these effect sizes and response rates--I guess this is either for the sponsor or maybe our pediatric colleagues--are these response rates comparable to what is seen with other treatments for ADHD or is there some differential response here?

DR. RUSSELL: Dr. Biederman?

DR. BIEDERMAN: I believe that the computed effect size is about 0.7, very similar to

the effect size of Strattera; lower than the effect sizes of the stimulants that are about 0.9. So, it is lower than the stimulants but potent enough to treat ADHD.

DR. WANG: Then this is actually a question for the FDA. The sponsor is already proposing warning language and I am curious what are the potential actions you can take. I mean, bolded warning; black box warning? Are those the same thing? Are there other intermediate warning language actions you can take? Because the sponsor is already proposing potential language.

DR. ANDREASON: I am sorry, I missed the first part of your question.

DR. WANG: Firstly, I should know this but is there a difference between bolded warning language and a black box warning? And, are there intermediates between them and what other options are there?

DR. ANDREASON: Yes, they are different. Which adverse event are we talking about here?

DR. WANG: They are already proposing

language for, it sounds like, psychiatric adverse events and also for skin rash.

DR. LAUGHREN: Well, there is a difference between bolded language and unbolded language in warnings. I mean, sometimes if we want to give particular emphasis to something we will bold it. That is different than a box. A box goes as the first thing in labeling and it is surrounded by a box. So, that is very different than just bolding language in warnings. So, there is a continuum.

DR. TEMPLE: In the context of the CNS warnings, you need to think about it in the setting of the consideration of all of the drugs that went on yesterday, and so on. The skin is their own baby. So, if we were very worried about it we could put it in a box. Usually you put things in a box when you want to be very sure that the doctor absolutely, positively considers this before prescribing it.

There are other things you can do. Ziprasidone, because of the QT prolongation, says you really think should think about using other

drugs before you do this. You can go further, you can say this is absolutely only for people who fail other therapy. Sometimes we do that even if we don't know for sure, as I said earlier, that it absolutely works in people who failed other therapy. You know, because of its different properties, you assume there might be a population that responds that way. There are a variety of things you can do to try to direct therapy. We like to say we don't practice medicine but we do sometimes try to influence the way a drug is used if we are worried about its safety. The black box is the loudest statement. There is at least a perception that it affects use because it scares people. That is why some people like it and some people don't like it. Bolding is more prominent than non-bolding, and so on.

DR. REESE: Dr. Leon?

DR. LEON: Dr. Biederman, I would like to clarify what you said about the Strattera effect relative to what we saw in this trial. It is my understanding that the Strattera effect size was

about 0.80 and in these data it was 0.56. So, this is quite a bit smaller. It is still a minor effect size but it is not as large as was seen in the Strattera trial.

DR. BIEDERMAN: To my knowledge, and I don't remember those numbers by memory, but I think between 0.6 to 0.7 is the effect size of modafinil. The company may have that information better than me. I understand as well that the effect size of Strattera on average is very much similar at about 0.7. In the meta-analysis of non-stimulants that Dr. Faraone did a relatively short time ago, that is shared by other non-stimulants as well, like tricyclics and things of that type, on the order of magnitude of 0.7, a low effect size of stimulants at about 0.9.

DR. REESE: Dr. Pine?

DR. PINE: I would like to go to slide number 89. I guess the thing that I am struggling with most, and I think a lot of people might be, is the dermatologic issue. On the one hand, I don't want to start a fight but, on the other hand, I

guess I am struggling a little bit with some of the inconsistencies in terms of the way three of the cases on slide 89 are being discussed. So, I guess what I want to do is point out what I see as the inconsistencies and then maybe hear from Dr. Bigby about do I have it right; do I not have it right; and then maybe also try to clarify some of those inconsistencies.

So, the way that I heard it is that case number 1 or patient number 1 everybody agrees had Stevens-Johnson but there is disagreement about the etiology, I heard, which confuses me a little bit because I don't understand what the etiology possibly could have been except for the medicine or except for the modafinil. So, I would like to hear discussion about that.

For patient number 4, at least what I heard was that Dr. Bigby did think it was Stevens-Johnson and I heard that two out of the three experts at Cephalon thought it was at least possible Stevens-Johnson. So, at least in the way I am thinking about it, I would think of those as

two at least likely cases.

Then, for patient number 5 I am a little blurry in terms of the magnitude of concern as a non-dermatological clinician. If I see a possibly suggestive hypersensitivity reaction or whatever Dr. Bigby classified it as, is that equally concerning, or slightly less concerning, or how much less concerning than Stevens-Johnson?

So, do we have three cases where everybody would agree that these are concerning dermatologic issues? Do we have one case? Do we have two that are somewhat concerning and a third that is suggestive? You know, can we get some agreement on that?

DR. REESE: Dr. Bigby?

DR. BIGBY: What I would say is that case number 62338 is a case of Stevens-Johnson syndrome and, based on the information that is provided, I would say it is drug related.

DR. PINE: What about the other two? For case 18004 would you also say that? And, what is the disagreement?

DR. BIGBY: I would say that that case is more likely to be due to something else other than a drug. So, I don't actually count that as a drug-related case. What was the third one?

DR. PINE: The third one was case 056003. You said fever, urticaria, swollen eyes, vomiting, increased ALT/AST and the Cephalon review said possibly suggestive of a hypersensitivity reaction--I guess level of clinical concern in terms of a serious adverse effect related to the medicine.

DR. BIGBY: You are going to have to give me a little time for that one.

DR. PINE: Okay. Dr. Goodman is whispering in my ear that he wants to know what made you conclude on case number 18004 that it was not medication related.

DR. BIGBY: For that case it is just not so clear to me what the diagnosis is. I mean, it is hard in sort of spottedly reported case reports to figure things out and I just am not convinced that that is a drug rash at all.

DR. PINE: Then I guess the last question, when I asked you before about your level of concern you seemed fairly clear that there is, quote, a signal here in terms of dermatologic risk. Based on what you just said, my conclusion would be that you are basing it on this one confirmed case out of 923.

DR. BIGBY: Plus, there is a signal for exanthems. Those aren't serious reactions but there is also a signal of exanthems occurring with the drug.

DR. PINE: But I also understood you to say that there is not necessarily a relationship between exanthems and incidence of Stevens-Johnson.

DR. BIGBY: This is correct.

DR. PINE: So, again, I guess what I am hearing is that it is really the one case out of the 923.

DR. BIGBY: I think that that is a good summary of how I feel about it.

DR. RAPPLEY: But there are also the four cases in adults. Is that correct?

DR. PINE: I think those were in adults.

DR. RAPPLEY: That is right, in adults.

DR. PINE: And it was consistent with the base rate. When we looked at the patient-years exposure it was consistent with the base rate of Stevens-Johnson syndrome, the four adults.

DR. REESE: Dr. Robinson?

DR. ROBINSON: Could we go to slide 112? I just want to clarify a few things because in Dr. Andreason's presentation it said that we were finding some dermatologic signal within the clinical trials but not in the postmarketing, and I just want to clarify a few things on this slide.

In the pediatric subgroup you didn't find a signal for rash in the postmarketing. Is that correct?

DR. RUSSELL: Certainly, in the postmarketing setting in children we have had no reports of any serious skin reactions. That would be correct.

DR. ROBINSON: Okay. Then, one of the questions about that is, is that because there is

none or is it that you are unable to detect that? So, that is why I would like to ask a question about the psychiatric signal that you do have in the pediatric subgroup because in the clinical trials it seemed that there is some signal about suicide and psychosis, and in the postmarketing data for pediatrics were you picking up that signal?

DR. RUSSELL: In the postmarketing data we saw seven cases that Dr. Stankovic highlighted for you.

DR. ROBINSON: That was in pediatrics?

DR. RUSSELL: That was in pediatrics, yes.

DR. ROBINSON: And it was which ones? Psychosis or suicide?

DR. RUSSELL: If I remember right, there were three psychosis, one suicidal ideation. Perhaps you can clarify?

DR. STANKOVIC: There were four cases of psychotic symptoms. There were two cases of aggression and violent behavior and there was one case of a suicide attempt. That was the patient

that overdosed and used modafinil as one of the cocktail drugs but it was not modafinil prior to the event.

DR. RUSSELL: Thank you for clarifying.

DR. ROBINSON: Thank you.

DR. REESE: Dr. Temple?

DR. TEMPLE: Back to derm., I think it would be helpful to be clear on what the appropriate denominator is because there seems to be one case everybody agrees on. This 933 number that has been used includes some very short exposures. Dr. Bigby can tell us what kind of exposure is enough, but let's say we wanted to say how many of those 933 or some of the people from the other studies had, say, at least two weeks or whatever the right amount is. That would help. Maybe it doesn't matter whether it is one out of 900 or one out of 600 but it would be good to have a number. So, how many people who were on it long enough to have had a nasty skin reaction actually were there for that one to be the numerator for?

DR. BIGBY: That is a very good question.

You know, I think that the best data available about the window of exposure where TEN/SJS is going to occur comes from that study that I cited. It was sort of a consensus panel in three countries, and the majority of cases occur within the first one to four weeks. It is probably one to three weeks. And, if you sort of include in your denominator patients that have been on it steadily for months and months and months you actually probably come up with a lower rate than the actual because the time that you are going to get it in is in that first month.

DR. REESE: We can have the response and then Dr. Armenteros.

DR. RUSSELL: I can get Dr. Shear to come up and comment on these cases with respect to etiology and all the other aspects we have been discussing.

DR. SHEAR: Thank you very much. From a dermatologic point of view from somebody who has been doing this for 20 years, first of all, I would like to thank Dr. Bigby for his excellent

presentation because I agree with what he said and this is an area that has been really messy over the years and you can see the confusion that led us here.

So, I would really focus on that one case of Stevens-Johnson syndrome. Going through that case extensively--the panel went through it but I also went through it with the panel again, with Amy Paller who was the leader of the panel--to try and figure out exactly what was going on with that case and how we could best characterize it.

I think we see enough to call it either Stevens-Johnson syndrome or maybe erythema multiforme major. You could then argue about which it is, and does it really matter since both of those can be viral induced? Speaking with the investigator and looking through the case records, there were clear viral-looking lesions that suggested Coxsackie very highly in the pharynx prior to the patient getting this. The clinical course was very compatible with a viral-induced either erythema multiforme major or Stevens-Johnson

syndrome because actually the patient was not that sick and was able to continue going to school and continue with other activities. Part of the problem was getting the full history, and much of it was retrospective and there was a language barrier, but the patient wasn't sick enough to be admitted to hospital or really to be seen very carefully during the actual event. But still, piecing it together, I would certainly put viral etiology well within the mix. I don't know what percent I would give it but, you know, drug is in there and virus is in there so it is not a completely clear case of either Stevens-Johnson syndrome nor is it a completely clear case that it was drug induced.

DR. GOODMAN: Dr. Bigby, would you concur?

DR. BIGBY: I think the patient had SJS.

DR. PINE: But the suggestion is that it could potentially have been Coxsackie virus induced SJS, which would be a very different thing. Again, I mean I get the impression that you do not think that that is likely.

DR. BIGBY: You know, it is really impossible, never having seen a patient, to do this. I don't think you should call things EM if the patient doesn't have typical targets. There is no description--the data is inadequate to be very dogmatic or firm about this. I mean, I would say that none of the dermatologists involved here would go out and have a big fight about what this case is because the description is just not good enough.

DR. SHEAR: Yes, I should mention that in one of the papers it did describe target lesions. So, that was helpful but, again, there are all these bits and pieces in trying to look at the source documents. From the source all the way to the narrative, you get different bits and pieces. Some are quite extensive. The MedWatch report has different data, but piecing it all together, there is uncertainty but it is in that EM major and Stevens-Johnson spectrum that overlap, if you will.

DR. GOODMAN: Hold your questions. We are going to break for lunch and come back at one o'clock. We will have the public hearing component

at that time.

[Whereupon, at 12:30 p.m., the proceedings were recessed for lunch, to reconvene at 1:00 p.m.]

A F T E R O O N P R O C E E D I N G S

Open Public Hearing

DR. GOODMAN: We are going to begin the afternoon proceedings. I am going to ask Dr. Pine to read the description of the process for the benefit of the individuals who are presenting at the public hearing segment of today's proceedings.

DR. PINE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, this financial information may include

a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. REESE: We will have the first speaker, who will have five minutes and when there is one minute remaining we will let you know your time.

DR. RAVENEL: Dr. Ravenel. As a pediatrician with 36 years experience--by the way, I have no financial disclosure; no connections; no funding. I am here independently as a private practitioner. With 36 years combined experience in academic and private practice with a heavy emphasis on behavioral pediatrics, I want to share some concerns with the committee concerning the pending new indication for Cephalon's modafinil, to be

marketed as Sparlon.

My concerns include the potential for abuse and diversion, as well as data questioning its effectiveness for ADHD, along with counterbalancing risk of adverse effects. Although being promoted as a drug with low potential for abuse, a substantial risk is actually suggested by the following: One, the FDA posted a warning letter on January 14, 2002 which compared the abuse potential of modafinil with that of methylphenidate in an inpatient study of individuals experienced with drugs of abuse. Quote: Results from this clinical trial demonstrated that modafinil produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate).

Number two, an Internet drug information database source states, quote: Modafinil may be habit forming. You should discuss the abuse and dependence potential of modafinil with your doctor.

Number three, as reported in "The New York Times," the United States Olympic Committee

includes modafinil in a list of banned stimulants and raises the spectra of widespread diversion and even more problem with, quote, lifestyle and cognitive enhancement and recreational use as has already been seen with traditional stimulants. Several psychiatrists and other professionals with experience with substance abuse by teenagers and young adults have warned that off-label use of this drug is, quote, staggering already, and warned that modafinil is very likely to become the next popular drug for its perceived cognitive enhancement or other perceived benefits enabling users to remain awake and alert for prolonged periods.

Marketing claims for the drug's effectiveness for ADHD appear to be exaggerated. A recent study in the Journal of Pediatrics of the American Academy of Pediatrics proclaims that at the final visit 48 percent of the modafinil-treated subjects were rated as much or very much improved compared to 17 percent of placebo subjects. One can see that 52 percent of subjects were not improved significantly. This compares to 75-85

percent comparable improvement on traditional stimulants. Insomnia was reported in 29 percent of the treated subjects, and it is noteworthy that drug tolerability was evaluated only by spontaneously reported adverse events. This can be expected to minimize adverse events significantly below their actual occurrence.

"The New York Times" article quotes experts as being concerned that manipulating natural sleep by reducing it may have serious consequences such as chronic sleep depravation damages health, immune system and is associated with life span. All of these references are provided in my speech.

The aforementioned FDA warning letter to Cephalon pointed out that the putative mechanism of action being claimed by the company was misleading, noting that the PI states that, quote: The precise mechanisms of action through which modafinil promotes wakefulness is unknown, period.

In summary, claims for potential effectiveness are exaggerated and the risks of

adverse events are minimized for a drug which has been shown to have a potential for abuse and for recreational use that far exceeds even that for traditional stimulants. Approval at this time for ADHD is premature considering the emerging controversy and public awareness of issues of adverse events, diversion and abuse related to stimulants.

It is ironic that this very phenomenon is being used by those promoting modafinil for ADHD. That is--

DR. REESE: One minute.

DR. RAVENEL: --looking at the problems with the stimulants. The FDA would be better served by exercising caution and by opening the door to even more of the same criticisms that have emerged recently about stimulant drugs. Thank you for your consideration.

DR. GOODMAN: Thank you.

DR. REESE: We will have speaker number two.

DR. JACKSON: If you could hold on putting

up the first slide, I might do those towards the end. Thank you.

My name is Dr. Grace Jackson. I am here independently as a private practice psychiatrist from eastern North Carolina. I am here today to actually begin by correcting some of the misinformation which has been disseminated to committee members over the past 48 hours.

The first point I would like to make is about some of the concerns I have as a doctor and who has actually worked in the prison system and as a former Naval physician. One of the first things I would like to point out is that I think that the precautions which should be described are basically the elephants that nobody seems to be looking at in the room. I would like to talk about some of those elephants.

The first elephant has to do with the fact that stimulants rewire the brain. This is what Harvard University and McLean Hospital clinicians have referred to as neuronal imprinting. Basically, what this means is that we shouldn't be

focusing just upon the potential for current diversion or current recreational abuse, but we should be looking at the fact that these drugs are altering the plasticity of the brain in children and adolescents in a way which increases the likelihood of future chemical dependencies, particularly to nicotine and to cocaine.

I would like to direct your attention to the papers by Nadine Lambert at the University of California Berkeley, papers published by Russell Berkeley in which statistical manipulations have been used to try to conceal this correlation, and also a recent publication from the University of Michigan which has demonstrated the same kinds of findings, that people who are arriving on college campuses who have received stimulants in middle school, high school or college have a 3-7 times higher likelihood of taking prescription stimulants illicitly, and a higher rate of actually using cocaine in the past year.

The second elephant that I would like to talk about which we haven't really been hearing

enough about, I don't believe, is the effects of stimulants on growth suppression. While it used to be the case that doctors took seriously the growth curve, it seems that this is now something which is casually dismissed. I believe it is time for the FDA and physicians to begin seriously considering the suppression of growth not only on the long bones of the legs and the arms, but also potential impact on the skull which continues development through adolescence and particularly the growth effects upon the brain, a point to which I will return in a few moments.

The third elephant I would like to talk about is the fact that no one yet here, at the FDA or at these hearings in the past two days, has discussed the effects of stimulants on cortical blood flow, specifically frontal cortex, parenteral cortex and temporal cortex. I believe that if you will actually pay attention to the medical literature there is a real vascular effect which actually deserves a black box warning, at the least, so that physicians and family members are

aware of the fact that these stimulants have the potential to shrink the cortex, especially the frontal cortex, and if they are not doing that, at the very least, they are not benefiting children who, some practitioners believe, begin life with smaller brain volumes initially.

The next point I would like to make is that we hear so much about the FDA needing to balance the risks and the benefits of drugs. Well, I would like to just point out the fact that I have heard numerous references to the MTA study in the past two days. Fourteen-month outcomes have been emphasized repeatedly. I would like to just say something that was misrepresented yesterday and again today. If you will actually go into a paper which was in the Archives of General Psychiatry in 1999, called "Mediators and Moderators of the Outcomes of the MTA Study," you will find about two sentences in that whole article where they actually have done a subgroup analysis of the children who began that study in an unmedicated condition and who remained in an unmedicated condition. Those

children actually had superior numerical improvements compared to the children who began unmedicated and were placed on stimulants. While that finding was not standardly significant, that may have been an effect of the study being under-powered.

Even more important though is the fact that in the Pediatrics journal, in the year 2004, 24-month outcomes were published for the MTA study. The findings at that point demonstrated that the effects of medication deteriorated; that the trajectories for symptomatic improvement reversed; and, in fact, the benefits of behavioral therapy--a modality that consisted mostly of one 8-week summer camp--actually had enduring effects.

So, I would like to suggest that this implies that a lot of the treatments that we are hearing so much about as being so necessary are, in fact, futile when one carries out the studies to a long enough duration of time.

Finally, I would like to return to the misinformation which continues to surround the

classification of medications that we keep hearing as they are not really stimulants; they are just central nervous system activators--

DR. REESE: One minute.

DR. JACKSON: I would like to suggest to the committee that they need to talk to the World Health Organization. Stimulants are classified not on the basis of potential addictiveness; they are classified as stimulants on their potential to be CNS activators. Actually, the World Health Organization classifies drugs on the basis of three properties: One, chemical structure. You ignore the fact that atomoxatine is a chemical derivative of phenylpropanolamine, a chemical structure which was removed from the market by the FDA in 2000 because it caused hemorrhagic stroke.

I would like to point out the fact that the World Health Organization also classifies stimulants on the basis of pharmacological properties, none of which require dopamine re-uptake inhibition to meet the criteria of being a stimulant, and I would like to see that everybody

drinking coffee here to recognize the fact that caffeine, which is an adenosine-2 antagonist, is not something that you would classify by Dr. Andreason's standards as a stimulant. Yet, I think Starbucks would say something else.

Finally, I would like to say--

DR. REESE: Time.

DR. JACKSON: Thanks.

DR. GOODMAN: Thank you very much.

DR. BAUGHMAN: I am Fred Baughman, a neurologist. I have discovered and described a handful of real neurological and genetic diseases. I am speaking on the chemical imbalance lie as it applies to modafinil and other ADHD drugs.

If one goes to a physician or takes a child or parent to a physician, if there is a gross microscopic or chemical abnormality a disease is present. If there are no abnormalities no physician should say that there is a disease. In psychiatry there are no physical abnormalities, which means there are no actual diseases and here we speak of the risk side of the risk-benefit

equation. Psychiatric drugs appeared in the '50s. Psychiatry and big PhRMA married and gave birth to the chemical imbalance lie. At a 1970 congressional hearing the chemical imbalance strategy was already in place. Lippman, of the FDA, argued hyperkinesis is a medical syndrome. In 1994 Leber, of the FDA, in a letter to me confessed no pathophysiology has been delineated. At the 1998 consensus conference William Kerry concluded ADHD appears to be a set of normal behaviors. At the consensus conference James Swanson reviewed anatomic MRI research, concluding ADHD subjects have on average 10 percent atrophy.

I challenged Dr. Swanson, saying why didn't you mention that virtually all of the ADHD subjects were on stimulant therapy? The research had proven 14 times over that the drugs, not the fictitious disease ADHD, had caused the brain atrophy. Caught in this lie, the consensus conference panel confessed, quote: We do not have an independent valid test for ADHD. There are no data to indicate that ADHD is a brain malfunction.

Unlike real epidemics, once psychiatric diseases are found not to exist, the epidemics flourish nonetheless.

In 2002 Castellanos published the one and only MRI study of an ADHD untreated group but, inexplicably, they failed to use matched controls, voiding the study. So, I would hope that this study is not referenced as the proof that ADHD is an actual disease.

While the FDA's Goodman acknowledged that claims that SSRIs correct serotonin and imbalance go too far, he had the gall to suggest, quote, this is reasonable shorthand for expressing that this is a chemical or brain-based problem. Saying any psychiatric diagnosis is a brain-based problem and that medications are normalizing the function is an absolute lie.

There is nothing more despicable than a physician or physicians who knowingly tell normal patients that they are diseased for profit--

DR. REESE: One minute.

DR. BAUGHMAN: --yet, this has become

standard practice throughout medicine and FDA, APA, AMA, AACP, AAP, AANCNS, AAFP. The right to informed consent universally abrogated must be restored. You are mandating the medical treatment of ADHD. Where is the proof that ADHD is a disease? Give us that reference, that citation right now, please. Give us the reference citation to the test that demonstrates an objective abnormality child by child, please.

DR. REESE: Calling for speaker number four.

MR. HANSON: Good afternoon. My name is Ben Hanson. I am from Traverse City, Michigan. In the interest of full disclosure, I suppose I should mention a few things. In March, 2000 I was appointed to the Michigan Department of Community Health Recipient Rights Advisory Committee, a state watchdog panel that meets in Lansing. I received no compensation for serving on this committee, other than mileage for travel expenses. Also, I am the Michigan contact person for Mind Freedom International, a non-profit organization which

advocates for the rights of individuals stigmatized by psychiatric labels. This is a volunteer position for which I receive no compensation. I am also a proud member of the International Center for the Study of Psychiatry and Psychology, icspp.org, and I was one of the principal organizers of yesterday's ICSPP press conference here, in the Hilton. It is possible I may be reimbursed for some of my travel expenses by ICSPP but to date I have not received one dime of compensation from ICSPP, which is fine. I am happy to do this work for free. Finally, I have been contracted on a part-time basis by another non-profit organization, the Law Project for Psychiatric Rights, psychrights.org, founded by Alaska's attorney Jim Godstein. To date, I have received a total of not over $1000 for various services like updating the mailing list, working on the web page, etc.

I want to make it clear that I am speaking on my own behalf today. I am not speaking for anyone else, including these organizations I just mentioned. I am here before you as a private

citizen, a taxpayer of the U.S.

I want to say a few words about the drug Sparlon, also known as Provigil, also known as modafinil. My interest in this drug began a few years ago when I learned that modafinil had been approved for treatment of a new disease called shift work sleep disorder. This interested me personally because for nine years, from 1995 through 2003, I worked for the Michigan Department of Natural Resources as a ranger in a state park located in northern Michigan. I worked the night shift, from 7:00 p.m. until 4:00 a.m. five nights a week. Basically, my job was to walk around in the woods after dark, which I loved because I love the outdoors. It was a dream job except for those hours and I never got used to it. I can testify to the fatigue, to the irritability, to the general clumsiness and inattentiveness which is caused by working those late night hours, especially that last hour from 3:00 a.m. to 4:00 a.m. The rangers call it the "dead hour," the dead of night when the whole world except you seems to be asleep, nothing

stirred, not even the crickets, not even the mosquitoes.

I can testify to this mental dullness. In fact, I would say if you work those hours and you don't grow a little groggy and a little clumsy, the only reason I can think is that you are probably on some kind of drug. I believe consenting adults should have the right to take any drug they wish but I condemn the FDA for endorsing a fictitious disease, created most likely by some pharmaceutical marketing department as a way to sell more drugs. What is next, FDA? Are you going to approve jet lag as an official disease? Perhaps it is only a coincidence but I understand the formulary patent on modafinil expires this month, March, 2006--a minor inconvenience to Cephalon and its stockholders. But one way around that problem would be to change the name of the drug, call it Sparlon and approve it for the treatment of ADHD, which is a larger market than shift work sleep disorder anyway. Isn't that what Eli Lilly did when Prozac's patent was about to expire? They

changed the color of the pill from green to pink. They changed the name to Sarafem and they marketed it for another invented disease, PMDD, and the FDA approved that. No problem.

I flew down here from Michigan--

DR. REESE: One minute.

MR. HANSON: --because I couldn't believe--I can't believe that you people are really going to approve this pep pill, which reportedly allows people to get by on two hours of sleep a night, for children diagnosed with ADHD. If you do this I want to be here to see you do it with my own eyes. Thank you for this opportunity to express my opinion.

Committee Discussion

DR. GOODMAN: Thank you. At this point I would like to invite our committee members to ask questions of both the FDA and the sponsor. At a time when I think it is probably the appropriate moment we will put the questions up on the screen, but before we do that let's have more free-ranging questions, including some that may have been

carried over during lunchtime. I remember that a few people didn't get an opportunity to ask their questions.

DR. REESE: Dr. Armenteros?

DR. ARMENTEROS: Yes, a question to the sponsor pertaining to the most common side effect in the list, which is insomnia, could you tell us a little bit more? For example, does this start happening in the very beginning? Do kids get used to it? Does it change during the time of treatment under observation? And, does it have anything to do with dosing?

DR. RUSSELL: In the main, the insomnia appears to start with treatment initiation, and the highest incidence of first reports of insomnia occurred during the first two weeks of treatment and then it does appear to taper off. As Dr. Stankovic mentioned, I think we had seven withdrawals from the drug because of insomnia. So, there appear to be people who either learn to get used to the insomnia or habituate to it, as with many of the other drugs that I think have this as a

side effect. I am sorry, I know there was a third part to the question but I have forgotten it.

DR. ARMENTEROS: Yes, what is the relationship to the dose?

DR. RUSSELL: We did look at the doses and there doesn't appear to be a major difference with the doses of 340 mg or 425 mg.

DR. REESE: Dr. Mehta?

DR. MEHTA: Actually, it is just a comment on Dr. Temple's earlier remark. All the studies are two-week or longer. There is only one study in 24 subjects which is a single dose. So, the denominator should be somewhere around 920 or something like that.

DR. GOODMAN: I have a question for the sponsor about the pharmacokinetics. If you took two children, same age, and one was being administered 400 mg modafinil, the other 200 mg modafinil obviously the plasma levels would be higher in the one that is receiving the 400 mg, but would the levels of the metabolite be proportionate or disproportionate to those levels as well? You

may have covered that and I may have missed it.

DR. RUSSELL: Yes is the answer.

DR. GOODMAN: They would be proportional?

DR. RUSSELL: Yes.

DR. GOODMAN: In a linear fashion?

DR. RUSSELL: Yes.

DR. GOODMAN: Thank you.

DR. REESE: Dr. Leon?

DR. LEON: Could the sponsor please show us a slide of the weekly retention rates? I notice there is a big difference between the LOCF results and the endpoint and I am curious to see how those retention rates look, and if there are differences. I know maybe about 50 percent more people dropped out of placebo than active medication.

DR. RUSSELL: The biggest time of dropout was between weeks three and five. This largely may have had something to do with the design of the protocol that did allow patients who were going to come off for an adverse event to roll over into the open-label program at that time. The reason for that allowance was based on a lot of input from

investigators who found that it would be difficult to keep children on a placebo for that length of time. So, there was a dropout between week three and week five.

DR. LEON: Do you have a slide that shows the weekly retention rates? Could we see that, please?

DR. RUSSELL: I am looking at my colleagues and they don't seem to have it.

DR. LEON: I didn't see it in the materials. Is it in the book maybe? It is pretty important when we are trying to draw inferences about efficacy.

DR. RUSSELL: I think in your briefing document there are by week numbers.

DR. LEON: I didn't see it. Maybe you could tell us what pages to look on.

DR. RUSSELL: Let me try and find the page. If you look at figure 4 on page 31 of the briefing document, there are the numbers for the CGI that are actually the numbers--sorry, they are not; I am misleading you. I am afraid we don't

have it.

DR. REESE: Dr. Wells?

DR. WELLS: I have a question about the source of the postmarketing adverse events that were reported, a question to the sponsor. These postmarketing events, do these come from all of the postmarketing studies, all events from all studies? Also, do they include voluntary reports from practitioners in a more naturalistic setting?

DR. RUSSELL: I am sorry, could you repeat the question?

DR. WELLS: The question is about the source of the postmarketing reports of adverse events. Where do these comes from? Presumably postmarketing studies are included of the drug used in other indications. Would it also include voluntary reports of practitioners--

DR. RUSSELL: Yes, it would. The spontaneous reports would be reports from healthcare providers, consumers. Any study that we undertake we include in our clinical trials information.

DR. WELLS: So, it is data from studies as well as voluntary reports from practitioners?

DR. RUSSELL: In the postmarketing it doesn't include the studies; it includes the voluntary reports.

DR. WELLS: Just the voluntary reports?

DR. RUSSELL: If I could clarify the previous question, on figure 3 on page 29 of the briefing document there are numbers at the bottom of each of the graphs.

DR. REESE: Dr. Pine?

DR. PINE: I guess two issues, and one of them I think maybe we will just come back to. That is the issue that Dr. Leon just raised about the sample sizes for each week on page 25 efficacy data. I realize you don't have it now but, you know, I think a few of us are a little concerned about differential attrition in terms of the efficacy data and it would be very helpful to see those data but, again, I know that you don't have that right now but maybe if you could get them and give them to us sometime in the next half hour or

so.

The second issue is a question on psychosis. I guess there are really two things that--yes, that slide, right there. If you could just give us the Ns in each group at each data point.

[Slide]

DR. RUSSELL: This is the ADHD rating scale. Actually, the numbers are here the teachers versions so you can see that there are dropouts as the weeks go by.

DR. PINE: Yes, they are very small.

DR. RUSSELL: They are pretty small. I am afraid I can't see those from here.

DR. PINE: You can barely make them out in the document but you can see them; they are there.

But the issue of psychosis, there was an extensive discussion about this yesterday, for people who weren't here and I don't know that we need to repeat the whole discussion. I guess I would just like to raise two issues. One is that I seem to recall on one of the slides from yesterday

that there was a hint--and I can't remember which event it was, that one of the adverse psychiatric events looked to be more prevalent in modafinil or Sparlon relative to the other agents. If somebody from the FDA could either point that out or bring it up, that would be helpful. Then I have one other point about that.

DR. GOODMAN: Which event was it? Dr. Mosholder would know. Do you remember?

DR. MOSHOLDER: Andy Mosholder, Office of Drug Safety at FDA. For the suicidal event category there were four events in my analysis of modafinil, zero on placebo. I wonder if that is the one. For psychosis there were two and none on placebo. Those are just the double-blind.

DR. PINE: And I guess my take on it is that I don't feel any differently looking at the data here for this compound than I felt about the broader discussion yesterday, on the one hand. On the other hand, I think it is important, particularly for people who weren't here yesterday, to know that similar concerns that were raised in

general for other compounds should also be acknowledged or discussed here.

I guess the last thing to say is that the quality of the adverse event reports in general always concerns me. But I guess on slide 102, case number 312592271 with 10 months of ideas of reference concerns me. I realize it is one case and I don't think we should make too much out of it, on the one hand. On the other hand, in terms of discussing the medication I do think that we need to at least bring up the point again that there needs to be some acknowledgement that these are potentially concerning adverse events.

DR. GOODMAN: As long as you are on that subject, Dr. Pine, it reminds me that in the review of the correspondence between the FDA and the sponsor there was a description of one case that seemed to be misclassified or mis-coded. It was an individual who was said to have had a personality change or personality disorder and, in fact, they had a noose around their neck. Could somebody from either the sponsor or the FDA side clarify?

Obviously, if you read a case like that it harkens back to early concerns we had about previous problems in appropriate reporting of those kinds of AEs.

DR. RUSSELL: Yes, I can comment on this case. This was a six year-old girl who after two days of discontinuing the drug--she stopped the drug on day 91 and then on day 93 engaged in what her mother calls bizarre behavior but there was some suicide intent by putting a rope around her neck. The patient was hospitalized. The inpatient assessment says that the patient had major separation anxiety and admitted to trying to hurt herself with grave references to suicide. This was a girl who had a history of mood swings and a family history including maternal depression and a suicide attempt. So, that is that case which was originally thought by the investigator to be abnormal behavior but, as you saw today, we included it on the slide with the suicidal cases.

DR. REESE: Dr. Bigby?

DR. BIGBY: I have a question about

response of the placebo group. You have a figure that was in the CD that you sent and it was a summary slide for the three studies looking at the ADHD rating scale school version for all three studies. I think it went out to eight weeks, and it is really striking how much the placebo curve drops down. Also, if you can find and put that slide up--I don't know if you have that slide, it has the numbers of people still in the study at the various time points.

So, I have two questions. The first one is for anybody who knows about ADHD trials. Is this kind of effect in the placebo group sort of universally seen in ADHD trials?

DR. RUSSELL: Dr. Biederman?

DR. BIEDERMAN: I am not sure whether I know what you are asking, but placebo response in ADHD is on the order of magnitude of 30 percent on average in the literature. You are asking if this placebo effect is typical of other studies of ADHD. It is pretty much within that range.

DR. BIGBY: Then, the second question I

think sort of goes back to the question about numbers of dropouts. Now, at each of these time points you have listed the number of patients in the treated and the control group. For the control group you start out with 210 and by the time you get to the seventh week there are 71. So, basically two-thirds have dropped out. Is the score with the bracket at each one of those time points just the people still in the trial, in which case the same would be true for the treatment group and it is sort of a per-protocol trial and not an intent-to-treat trial.

DR. RUSSELL: Depicted on these figures is the by week analysis so those are the patients that are actually in the study at that particular time. The endpoint is the last observation carried forward analysis so all values are included in the endpoint analysis.

DR. REESE: Dr. Wang?

DR. WANG: Yes, I want to explore some more this differential in effect size between modafinil and other ADHD treatments. Particularly,

you mentioned Strattera. What I am interested in is the clinical significance of that decrement. Is this decrement of clinical significance? Is it of a size where it would warrant making modafinil a second-line treatment? I think it will have some bearing on how desirable we think it is to warn about the safety issues.

DR. RUSSELL: The overall effect size across all three studies was 0.69.

DR. WANG: I am talking about the differential between the effect size in your pivotal trials and what is known about the effect sizes for other ADHD treatments and what is the clinical significance of the difference.

DR. PINE: Can I ask a question about that 0.69? That is a Cohen's D for the difference in active versus placebo? Is that what that difference is?

DR. RUSSELL: Dr. Kingsbury, can you comment?

DR. PINE: You know, typically most people go by Cohen's D criteria so stimulants have Cohen's

D effect of somewhere in the low 1s, 1 to 1.2. Strattera I think is frequently quoted as 0.7 to 0.8. So, if it is 0.7, if that is a Cohen's D for the difference in the change of active that accounts for placebo and that would be a reasonable effect size. But I would like to hear if that really is the effect size they are quoting.

DR. KINGSBURY: Specifically calculated as the difference in treatment effect divided by the pooled estimate of the standard error.

DR. PINE: The pool of the placebo?

DR. KINGSBURY: The placebo.

DR. PINE: So, that is a reasonable effect. It is not huge but it is within the realm of an effective agent.

DR. WANG: Would you say it is getting to the point where this would be a second-line treatment?

DR. PINE: I would not say that. Clinically, based on an effect size of 0.69, I would not say that that would make it a second-line agent necessarily. It is clearly less than what

you would expect in stimulants but I would think about it similarly as I would about atamoxatine.

DR. LAUGHREN: I think if you are going to be comparing effect sizes for different drugs you ought to be looking at it in the same trial because it varies a lot from trial to trial. It is going to depend on the sample size and on the placebo response. So, I think it is really hazardous to compare effect sizes, whatever measure you are using, whether it is Cohen's D or anything else, to cross-study comparisons.

DR. PINE: On the other hand, since we all know of multi-drug trials where people obviously are grappling a little bit with the efficacy data I think we have to say something about, you know, in the universe of studies of ADHD, is this in the realm of a reasonable treatment or not. Again, I would agree; I wouldn't quibble with what you said.

DR. WANG: And I am not arguing. I am just trying to kind of qualitatively understand whether if there is a warning, whatever shape or form it takes, and it drives down use or

effectively turns modafinil into a second-line treatment, is that a terrible thing? Is it a good thing? Is it neutral? That is what I am trying to kind of understand.

DR. REESE: Dr. Rappley?

DR. RAPPLEY: I want to go back to the skin issue so if anybody else wants to talk about the effect--keep going? Okay. I would like to ask Dr. Bigby if he might have some insight about how we might think about the spontaneous reports of Stevens-Johnson syndrome and how that compares to the actual incidence.

DR. BIGBY: Actually, that is a very good question. Neil actually did a study in Canada where he ascertained cases of TEN, and he can give you the details of the study, and compared it to the spontaneous reporting system they have in Canada. I think that it is vastly under-reported. I looked at that paper last week and I think it was 10 percent or less than the cases that he found that had actually been reported. I think the same is true for other researchers that have looked at

reporting of TEN vis-a-vis drug usage in an attempt to try to determine rates of reactions.

DR. SHEAR: That is correct. We tried to look at patients with TEN and contacted burn units across the country to see patients who were coming in versus what was actually reported to Health Canada through the spontaneous reporting system, and we came up with a number of around 10 percent that were actually reported. So, we realized it wasn't necessarily the burn doctors but probably hospital pharmacists who were reporting it or other healthcare professionals but still it was about a 10 percent reporting rate.

DR. REESE: Dr. Pfeffer?

DR. PFEFFER: Again a clarification, Dr. Bigby. Maybe you can help us. You said that the Stevens-Johnson was dose related.

DR. BIGBY: No, no.

DR. PFEFFER: Then if you could clarify a little bit more about the onset of this type of skin problem.

DR. BIGBY: I mean, I think SJS and TEN

are idiosyncratic hypersensitivity reactions. I tend to shy away from talking about mechanism because I don't think anybody really knows what the mechanism is. Developing the disorder I think is not dose related but the point I was trying to make about the dose perhaps being a factor is that I am aware of at least two studies that have shown that the patient prognosis is better if the drug is identified and stopped, and it has mostly to do with the half-life of the drug and the body's ability to clear the drug. I think that if you start with a greater concentration it will take you longer to have undetectable levels and it might affect prognosis. I don't think it has anything to do with the incidence.

DR. PFEFFER: One other question about the syndrome, if a child develops this on a medication such as modafinil, would that child be at increased risk in the future for the syndrome? In other words, would the exposure to this particular drug increase the risk or would that not be an issue?

DR. BIGBY: Increase the risk if they were

exposed to any drug?

DR. PFEFFER: Either any drug or whatever causes the syndrome, yes. Does it lead to sensitization?

DR. BIGBY: Well, the only definite thing that i can tell you is that if they got the same drug again it might be that they would have the same reaction. Whether it identifies them as someone who is more likely than the general population to do develop TEN to other drugs, particularly drugs that are known to be associated with TEN, I can't answer that question although there is some suggestion, not entirely convincing, that that might be the case. But it is not clear to me that the exposure to the drug and the fact that they developed the TEN as the cause of that identifies them as someone who has that potential. So, I don't know if I am answering your question. I think that a patient that develops TEN to a drug--there is some evidence that they are more likely to develop that type of reaction to drugs. But I think probably they were that way before the

exposure.

Actually, again, this is a subject that Neil has done more work on than anyone I know. I mean, I think it would be useful for you to hear his comment on it as well.

DR. SHEAR: Thanks, Michael. It is a difficult question because you are not going to get enough data ever to really do that, especially if a child has had TEN. For every drug they get in the future the parents ask can this drug cause TEN, it is no longer a hypothetical possibility and if the answer is yes, but don't worry that couldn't possibly happen in a billion years, you know they are not going to get the drug. So, you are not going to collect that data.

What we did show was that among the aromatic anticonvulsants there was a risk of cross-reactivity and that is even hard to explain structurally. We don't know why that is but we showed in vitro and in vivo that it does seem to exist. But otherwise, usually people who have had Stevens-Johnson don't get it again.

DR. REESE: Dr. Malone?

DR. MALONE: I know you said that dose probably was not related to Stevens-Johnson but I guess it is a similar question, is there any mechanism that will explain why a group of children getting 340 mg of the drug might have a higher rate of Stevens-Johnson than those being treated for daytime sleepiness getting 200 mg or less?

DR. BIGBY: The only thing I can do is repeat I don't think the development of TEN, as far as anyone knows, is a dose-dependent phenomenon.

DR. GOODMAN: I think you are being appropriately cautious but there is the other factor we discussed of the sulfone metabolite. Although there is no proven relationship, there is certainly a suggestion based upon other compounds that have been associated with Stevens-Johnson that have that sulfone group. So, is it at least conceivable or plausible that the higher levels of that metabolite could pose a greater risk for development of Stevens-Johnson syndrome?

DR. BIGBY: Is it conceivable? Yes. But,

I mean, I think the threshold for whatever it is that is the mechanism for developing TEN is exceeded by all of the doses that you are talking about here. I mean, yes, what you said is hypothetically true. The problem is I don't have any evidence to say that it is or isn't.

DR. VAUGHT: Mr. Chairman, if I could address that for you, please?

DR. REESE: You may.

DR. VAUGHT: Thank you. What I would like to do is just perhaps orient the panel a bit.

[Slide]

Because of the inference of the sulfone to agents that have been directly associated with the occurrence of SJS--I am not going to do a chemistry lecture today but on the right-hand side of the slide is the modafinil sulfone. With the structural characteristics there is, in fact, a similarity across two agents that have been directly related to SJS. Obviously with the sulfa drugs and the aryl-sulfonamide valdecoxib, the only similarity is the sulfone group. I think what you

will notice is--and I agree with Dr. Bigby that while the mechanism is not well-known, in general with the sulfa drugs the amine group becomes activated and it is believed to be one part of the overall syndrome that is created, as well as the fact of the close association of the sulfone group to the aromatic ring. Valdecoxib is similar to this in that it has a sulfonamide group again associated with the phenyl group. While this is not a conclusive relationship, there seems to be a very broad preponderance of this type of structural feature being associated and directly related to SJS. We can see that with the modafinil sulfone moiety this is structurally simply not similar to these agents.

DR. MANNHEIM: We have a similar slide I would like to show.

[Slide]

DR. CAVANAUGH: We also looked and I have to say I am very impressed with the level of discussion today from everybody. When Dr. Mannheim asked me about Stevens-Johnson and I heard that

there was a sulfone, I said, well, you know, sulfonamide, as you know, is classically thought of and it is in the labeling. Sulfonamides in general are labeled as 0.1 to less than 1 percent. You can again see the sulfone here with the amine, and that is the sulfonamide; this is sulfanilamide and you can see it here and, again, sulfamethoxazole.

As you pointed out, there is some similarity with the sulfone but the amine is separated by two carbons and there is also a ketone here. If you look at sulfacetamide, and here you see a 3D structure rendering so you can see it a little clearer with the two oxygens, two carbons separated, a third oxygen and then the nitrogen which is going to be withdrawing electrons. If you look at sulfacetamide, the difference is that instead of the nitrogen being on this side, it is basically substituting for this carbon. So, this is a sulfonamide but it has a third oxygen, it is a third atom away. The interesting thing about sulfacetamide is that it has been reported to cause Stevens-Johnson, at least in the labeling, at 3

percent--I believe it is in the labeling; it might be in other places--and that is an eye drop. You know, people have died with even the first dose of eye drop where they have a history of sensitivities to sulfonamide.

So, you know, this whole issue of is it the sulfone, isn't it, I think what you have been hearing is that it is very, very muddy. We don't know. You have heard factual information and we don't know. The same with the dose. It is too small numbers. We don't know. It is plausible. Is there cross-reactivity? Maybe yes, maybe no; we don't know. So, these are some of the issues that we have been struggling with and I am glad the committee is dealing with them.

[Slide]

Let's see, was there any other point I wanted to make? The only thing that I wanted to point out is, you know, we have been talking about Stevens-Johnson and there has been talk about other hypersensitivity reactions, and I went through the various cases of rash and you heard earlier about

the PK and the exposures not being any different, and that is about what you would expect. But a lot of those rashes also were just general rashes. When you look at cases that could be possible hypersensitivity, you have several cases of allergic reactions. You have the vesiculobullous possible SJS. You have increased LFTs. One of them was a hypersensitivity. You don't have anything up here in the teens but it also could be due to the numbers. But in general the percentage for possible hypersensitivity is kind of consistent.

[Slide]

These are the individual cases and you can see the combination of symptoms. Here is an allergic reaction. Here is an allergic reaction with nothing else. Here is an allergic reaction with a rash. Here is the increased LFTs with eczema and that is the individual--oh, I am sorry, here is the increased LFTs with edema and urticaria and that is the individual who was 17-fold higher. You also have hives, fever, whatever. So, there is

some evidence of additional hypersensitivity. We are just arguing about numbers at this point in time.

DR. GOODMAN: That is helpful. Thank you very much. I have a more global question for anybody on the FDA side about the safety data. Is the FDA in general satisfied that there is sufficient long-term safety data at the doses being used for the pediatric population? We have focused a lot on the acute trials, individual areas of concern, but just in terms of a kind of more panoramic view do we have sufficient long-term safety data at this point for this dose in this population?

DR. LAUGHREN: I think I remember from the earlier slide that we now have about 240 patients greater than six months. Is that right? That is about as much as we usually have. Again, this is not a new compound. If there were some adverse event that we thought was related that had a long latency we might be more worried about it. I think the event that we are most concerned about here is

one that probably has a short latency.

Questions to the Committee

DR. GOODMAN: That satisfies me. I would like to turn to the questions, if we could have those projected. There are two questions for which we must take a vote. The first question is has modafinil been shown to be effective for the treatment of ADHD in children and adolescents?

Number two, has modafinil been shown to be acceptably safe in the treatment of attention deficit hyperactivity disorder in children and adolescents?

When we get to number two I would like to break that down in the following way, starting first with dermatological issues because those have been the most salient features; then with cardiac, growth and psychiatric. Let's begin with the first question pertaining to efficacy.

I think I already shared my view earlier and that has not changed, that I am satisfied that there is sufficient efficacy data as we have heard. You know, we don't have a direct head-to-head

comparison with an active comparator. That is unfortunate but it is not an atypical situation. When we have looked at the effect sizes, I think most of the experts in the room said it is probably not quite at the level of the stimulants. It is probably closer to the range of Strattera, yet it is still quite effective and has certain features that I think would make it a valuable addition to the armamentarium. I just shared my opinion but I want us to have a discussion and hear from around the room, from all of you, regarding the efficacy question. Anybody can volunteer.

DR. REESE: Dr. Wang?

DR. WANG: I would just second that one caveat about the comparative efficacy. I think it would be useful to have additional data just to understand where in the armamentarium this would fall. That is number one.

Number two, another big area of a question mark is the dose. I think it is unfortunate and it would be helpful if there were more data to suggest whether you have fathomed the lower bound of the

dosing range because, as Dr. Bigby said, maybe the development of these skin rashes isn't necessarily dose dependent but the prognosis may be dose related. So, getting kids on the smallest dose possible would be optimal. I don't know if this is additional trials but some way to understand if a lower dose might be useful.

DR. REESE: Dr. Pfeffer?

DR. PFEFFER: I share that idea and concern and I asked the question previously. It seems that trial 309 was a fixed dose and is the dose that was proposed, which was the higher doses. Trial 311 was a flexible dose and it looked to me, in slide 53, that there was demonstrated efficacy early on and I am assuming it is at a lower dose. Then, on slide 54, while it was a flexible dose we heard that it was a very rapid increase of dose early on. So, there wasn't enough sense in that trial if a lower dose might also have been effective.

So, while I think there is definitely demonstration of efficacy, the efficacy is

demonstrated on the high dose and the question about would a lower dose serve the purpose is not answered clearly.

DR. REESE: Dr. Temple?

DR. TEMPLE: Well, I think it would be helpful if, maybe with another look, you took a look at the Phase 2 study that led to the conclusion that you need the high dose, number one. I mean, we press people for dose-response data all the time but apparently we were satisfied that that had ruled out usefulness of lower doses.

The other thing to do is look at the average dose or maybe even dose groups in the titration studies to see whether, while the dose is still quite low, there is some separation. I mean, that wasn't the planned analysis but the company may have that. Early on there is not much separation so at least for the earliest part of the titration you really don't see much. Then at either three weeks, four weeks, five weeks you do, but we don't know the doses or the average doses or the subsets of dosing by that time. So, perhaps

one could look at that and see if we have an answer already.

DR. REESE: Dr. Armenteros?

DR. ARMENTEROS: That is fine, but it could also be an artifact of the time lag between administration of the drug and response.

DR. TEMPLE: I totally agree. If you didn't see something you wouldn't really know whether a lower dose might--but it was the Phase 2 study that I think is what convinced the Division that the dose-finding was sufficient. So, I think if you don't think that is adequate we need to know why.

DR. REESE: Dr. Pine?

DR. PINE: I guess just briefly to second some of the statements, it looks at least to me fairly clear that there are not a lot of questions about efficacy. It sounds like the data have been reviewed a few times. Just in looking at the three studies, on the face of it there can be a reasonably strong case made for efficacy here, and I don't know that I have a big need to discuss it

much further although I would be happy to hear other people's thoughts.

DR. REESE: Dr. Rappley?

DR. RAPPLEY: Speaking from the point of view of a clinician, I would say that this is a medication that looks to be somewhat less effective than the other options available to me to treat attention deficit hyperactivity disorder, and it has the common side effects, common and mild side effects that are very similar to the other agents. So, it would probably be perhaps a fourth or even a fifth line of medication that I might turn to in order to treat a child who was not responding to the other medications.

DR. GOODMAN: I wondered if you would revise that positioning of the medication if you had a sense of abuse potential, diversion potential. We can talk about that a little bit more today, but I have heard a variety of different views on this. It would appear that the abuse potential is less than with some of the stimulants but it is certainly true we often don't find out

about abuse potential until a medication becomes widely available in a particular population. So, I was just wondering if you might revise that if you felt that the abuse or diversion potential was less.

DR. RAPPLEY: Well, I would like to answer that in two ways. One is that we have heard that one reason a physician might want to use this is so that the physician would not have to deal with controlled substances. I don't like that argument. That is not about what is best for my patient in terms of their condition and their treatment. That is about a system that makes it difficult for me to deliver care effectively. So, I would rather educate my families that this is not a narcotic and it is controlled for some legitimate reasons and it is the best set of medications I can use and, therefore, I will work with that. So, I don't see that as persuasive.

The other suggestion that it would be less likely to be abused as an agent itself, I think that might be attractive to me if, in fact, I was

looking at a family where I thought abuse by other family members or my patient was possible, which is not an unusual case for my practice. But I have other agents in the classification of stimulants that I could turn to for that purpose.

DR. GOODMAN: Other comments on the issue of efficacy before we take a formal vote? Dr. Temple?

DR. TEMPLE: I am actually embarrassed to have to ask this, but outside of maybe psychiatry this Cohen's D is not widely used. Could somebody dilate on that a little bit? To divide effect size by some kind of measure of variance seems to give you something that doesn't have tangibility.

DR. PINE: It is not dividing the effect size. Maybe Andy can talk more about this. It is dividing the mean. So, it is a difference in means divided by pooled standard deviation. It kind of goes back to the in the social sciences, in a widely cited book in the mid '80s, about statistical power for that particular metric, which was the difference in means divided by the pooled

standard deviation in the two groups. Standards were kind of put forth that were somewhat arbitrary at the time, in the mid '80s, for a small, medium and large effect. And, there are standard deviation units so up to 0.3 was a small difference; from 0.3 to 0.8 was medium; and above 0.8 was large.

Then, what has happened over the last 15 years, particularly among pediatric psychopharmacologists but also adult psychopharmacologists, is that those standards have been applied and they tend to fit in terms of how people think about medications clinically. Typically, medications that physicians tend to think about as powerful tend to have large standardized differences or a difference in standard deviation of approximately one unit between an active treatment and an inactive treatment. Similarly, medium treatments tend to follow in the 0.5 to the 0.8 range.

DR. TEMPLE: It sounds, for example, like making your study larger makes your effect size

look bigger.

DR. PINE: No, it will not.

DR. TEMPLE: Won't decrease the standard deviation?

DR. PINE: No, it will not do that. In fact, one of the nice things about the Cohen's D is that it is independent of sample size.

DR. TEMPLE: We will talk off-line.

DR. GOODMAN: Other comments before we call the vote?

[No response]

In that case, we are voting on the first question on efficacy. We have three options, yes, no or abstain. Let's start with Dr. Mehta. Although officially his vote doesn't count, in my mind his non-vote is extremely persuasive.

DR. MEHTA: On this drug it is not an issue but I think it is a pleasure not to be able to vote on most of the drugs! I think there is clear and persistent evidence of efficacy so efficacy-wise I don't think I have an issue.

DR. MALONE: I don't have any issue with

efficacy either. I think that all the studies were positive and overall it looks effective.

DR. REESE: Ms. Dokken?

MS. DOKKEN: Yes on efficacy.

DR. REESE: Could you say your name before you give your vote? Thanks.

DR. WELLS: Barbara Wells, yes.

DR. ARMENTEROS: Dr. Armenteros, yes.

DR. PFEFFER: Dr. Cynthia Pfeffer, yes.

DR. ROBINSON: Delbert Robinson, yes.

DR. LEON: Andrew Leon, yes.

DR. PINE: Danny Pine, yes.

DR. GOODMAN: Wayne Goodman, yes.

MS. BRONSTEIN: Jean Bronstein, yes.

DR. WANG: Phil Wang, yes with those two caveats earlier.

DR. RAPPLEY: Marsha Rappley, yes.

DR. BIGBY: Michael Bigby, and if you really want my opinion about the efficacy of a psychiatric drug, yes.

[Laughter]

DR. GOODMAN: Do you want to recap for us

Cicely?

DR. REESE: Well, "the yes" have it. It is unanimous.

DR. GOODMAN: Let's turn to question number two, which is a bit more thorny--

DR. BIGBY: Could I ask a question?

DR. GOODMAN: Who has a question?

DR. BIGBY: Me. Is there a definition for acceptably safe?

DR. GOODMAN: It is the same that you would use in dermatology!

[Laughter]

DR. REESE: Dr. Temple?

DR. TEMPLE: Well, this goes back to the law and various elaborations of it. What the law asks is that safety be assessed by all tests reasonably applicable--a very broad standard that you could drive any sort of truck through; and that it show the drug to be safe for its effective use, which has generally been interpreted to mean that the benefits appear to outweigh the risks. But it goes on to make it clear that something can be

unacceptable either because it shows something bad or because you haven't done enough. We have elaborated on that in various risk management things but it is always the same--have you done what you need to do or enough of what you need to do? A judgment call obviously. And, can you conclude that in light of what it does that is good for you, you have acceptable risk? That is what it always means.

DR. GOODMAN: As we return to this question, I would like to break it down to different categories. Let's start with the dermatological issues first. I wonder if I could turn to you, Dr. Bigby, to offer your opinion on whether you think this drug is reasonably safe in this population, given what we have heard today about possible dermatological complications?

DR. BIGBY: I think that the drug should be put in the context of other currently available, marketed and highly used drugs where over time it has become clear that they are associated with the development of severe adverse skin reactions, such

as TEN and SJS, and I think that this drug will find itself among that group.

DR. PINE: Can I ask you a question about that? I actually found, and I don't know what the number of the slide is from Dr. Andreason--I found the slide that gives the labeling of Lamictal interesting and relevant and I wondered if you might comment on that. For Lamictal it says Stevens-Johnson syndrome--it gives 8/1000, that is what it gives in children. It is page 8, on the bottom. Because I do think your comment about placing it in the context of other medications is very helpful and lamotrigine is a medication that there is some familiarity with and I wondered if you might comment on the comparison. It has a black box below age 15, lamotrigine. Is that right? I think that is right. That is my recollection, anyway.

DR. BIGBY: You know, the problem that I think you are going to have is that you are going to have a difficult time coming up with and agreeing on a number, but I do think that the drug

should be labeled as one where people should be aware that it could be associated with SJS/TEN. Actually, I am quite surprised at the 8/1000 number because you are pretty close to one percent. You know, that is a pretty high rate for TEN. So, I don't know, I mean, I have a hard time believing that the number is really that high. Is it really that high?

DR. PINE: I don't know. I am just looking at what Dr. Andreason--

DR. GOODMAN: The numbers have come down over time. Is that correct?

DR. ANDREASON: Well, it is hard to say. If you look at the prospective registry study that was done, there was one death of Stevens-Johnson syndrome in that prospective registry with 1983. So, the idea that it is more common in children than in adults is fairly well accepted. I think that the numbers are reasonable from what we know. I think they are reasonable estimates.

DR. GOODMAN: It was placed in a black box and even though over time it would appear that the

incidence is lower for lamotrigine it has maintained its black box position. Is that correct?

DR. ANDREASON: I am not aware that the numbers have actually been documented to come down.

DR. TEMPLE: But if you had one death in a thousand people you wouldn't remove the black box. That is an impressive number for most drugs.

DR. GOODMAN: Dr. Bigby, I have a follow-up question too. I agree with your position but I just want to clarify the basis of it. It seems like it is largely on one case, one case in which you have fair degree of suspicion or confidence that there is a bona fide case of Stevens-Johnson syndrome and, given the denominator, that was enough for you to be concerned. Is that fair?

DR. BIGBY: Yes.

DR. GOODMAN: And there was some exanthem as well.

DR. BIGBY: That is fair. I mean, that is a fair statement of my position.

DR. GOODMAN: Let me just follow up then. There is this disconnect that we have all talked about--the real concern here is the extrapolation to large numbers and there is the disconnect with the postmarketing surveillance. But it would seem to me that that could in part be explained by dosing. I think I understand that dosing may not determine the incidence but it may have played a role in the persistence of the problem. So, we don't know whether the sulfone metabolite is relevant or not, nevertheless, we don't have a lot of postmarketing data in that age range at that dose and that could, indeed, explain the lower than expected rate in that population, in my mind at least. I just want to see others' reflection on that position.

DR. BIGBY: Can I just make a comment? You know, I have been involved in quite a few of these discussions about incidence of side effects postmarketing, and one of the things that is really striking about postmarketing studies is that unless they are very rigorous they don't detect much. So,

when you are relying on spontaneous reports I think that you are going to miss a lot of the cases that were, in fact, cases and it is striking how poor, in terms of pickup of adverse reactions, postmarketing studies are unless they are really done with some sort of design in mind.

DR. TEMPLE: Obviously a problem is that nobody can answer the question of what the degree of under-reporting is and it is estimated widely. However, there is a lot of reason to think it is less bad when events occur that are likely to be drug related. So, for example, we have been pretty good at picking up acute hepatic necrosis in cases like that because when that happens the drug is highly suspect. When we approved a drug that was a major 3A4 inhibitor we got cases of rhabdommyolysis because it inhibited the metabolism of a couple of statins. We get cases very rapidly. Now, I don't know whether we got them all but these kinds of things you probably do better than things that happen regularly in the background--seizures, things like that--where why would a person decide

that the drug did it. So, it is not that discouraging for things that are obvious and that deepens the mystery to me because, you know, the fact that the dose is about half what you would recommend now, that doesn't make it seem like there shouldn't be any cases. I mean, that is why it is here, because we find it a little surprising that there are no cases and yet there was one.

DR. CAVANNAUGH: In terms of your question, Dr. Andreason showed a slide where he estimated about 11,000 children 6-12 years old who were probably getting modafinil from the postmarketing experience. If you take that 1/900, that is just about 0.1 percent. So, if you take 0.1 percent of 11,000, that would be about 10 cases.

Now, it is commonly quoted that reporting rates are about 10 percent. That is based upon drugs where they may have been on the market a while but, all of a sudden, somebody publishes an article with a case-control series and then everybody else starts reporting it. In that case,

after people are, you know, kind of all reporting cases, that is where you get the 10 percent. You know, if you even took 10 percent of 11 cases or 10 cases you might expect one case to be reported.

Now, yesterday you heard that psychosis and aggression was about one percent consistently with the various drugs used for ADHD. Back in June, we also discussed this with Concerta specifically and you have about 1.25 million kids on Concerta and we know now that it is about one percent in terms of psychosis. Yet, you were dealing six months ago--say, one percent out of 1.25 million is 1250 and yet you were only dealing with--I can't remember the number but maybe 30 cases. So, it was less than one-half of one percent that was the reporting rate.

MS. BRONSTEIN: My question is to the FDA. What kind of requirement does manufacture of Lamictal have for postmarketing studies and reporting of incidence?

DR. ANDREASON: I am not sure what the requirements are. Right now, they have already

completed the registry study. That is in labeling. There is already a black box. I think that the risk has been capped. I am not sure exactly what more one would want. It is also noted in the black box that it is only approved in children for Lennox Gasteau even though it is approved for other things in adults. I think that is about all we could expect.

MS. BRONSTEIN: Thank you.

DR. REESE: Dr. Laughren?

DR. LAUGHREN: I want to come back to the point that Dr. Cavanaugh was making. I think there is a real problem in knowing what the extent of under-reporting is and it probably varies so much depending on what the event is. With something like psychosis, especially depending on how you define it and if you are defining it just as hallucinations, a lot of those probably aren't going to get reported because it is a fairly common event in the background. Something like Stevens-Johnson, which is an extremely unusual event, a very alarming event, is probably much more

likely to get reported. But the truth is we don't know what the extent of under-reporting is so you have to factor that into this. It is hard to know what it means that you don't have any reports among roughly 35,000 kids who have been exposed to it postmarketing but it is a disconnect and you just have to figure that in, in your overall deliberations on this matter.

DR. REESE: Dr. Mehta?

DR. MEHTA: I think it is just a comment to Dr. Cavanaugh too, essentially reiterating what Dr. Laughren said. I can't believe that 90 percent of the Stevens-Johnson syndrome which occurs in patients, either in Europe or in this country, is not reported.

DR. ANDREASON: Also, those numbers on exposure are unique patients between the years 2002 and 2005 only in the United States.

DR. REESE: Dr. Temple?

DR. TEMPLE: This is right at the heart of all this. If you really believe the one case is likely to be drug related you are talking about a

rate with a point estimate of something like 1/1000 and a lower bound that is a lot worse than that. That is one problem.

One question is how reassured to be by the fact that the pediatric use in the outpatient setting hasn't produced any, and I guess if you follow what Dr. Cavanaugh said you shouldn't take any reassurance from that at all because people report so poorly. My own view is that I take a little bit of reassurance but it is very hard to know. But that is what is at the nub of this. Just to make it obvious in case it isn't from the questions, the things you can do is try to manage that risk, taking some estimate of it, or ask for more data. That is the question. That is what question two is about.

DR. PINE: I guess thinking out loud a little bit, and in many ways my comments are similar to what Dr. Temple just said, I think if you listen to anybody who knows about dermatologic issues and who has talked about it today there is clearly a concern among everybody I think--you

know, the sponsor's dermatologist was concerned; Dr. Bigby is clearly concerned. I guess the thing I am struggling with is, you know, what is the level of concern. I think the other thing we would say, and I think everybody would agree with this and Dr. Bigby himself said this, that we really do not have enough data clearly to specify what the level of concern would be because there is this one case out of 923 but, when pushed, I totally agree with what you said, that you haven't examined the patient.

So, I guess what it brings things down to and it makes me somewhat uncomfortable is that there is a lot of judgment call going on here for a potentially incredibly important decision. I just feel somewhat uneasy with that because, you know, you miss it either way and you could screw up big time. I don't know if that says we need to get more data. I don't know what that says but it just seems to me that we are stuck in a way.

DR. GOODMAN: Let me take it from there. So, I think the real question I would like to

discuss now about this issue among the committee is whether it warrants a black box for that concern about Stevens-Johnson syndrome. I think that is really what you are alluding to there, Danny. We have efficacy. We have agreed upon that. We have already voted it. We have concerns about Stevens-Johnson but we have only one case that we can really hang our hat on. We don't have the postmarketing yet. It might be appropriate use for a black box given that it is something that will alert the prescriber and the patient to recognize it early. I think it is that early recognition that could make a difference in terms of outcome.

I am not emphatic about it. I think that there might be other ways of addressing the warning without it being put in a black box because we have so little data at this point. Perhaps the highlighting would be a step below that. There is no question I think at this point that it should be included among the warnings. So, it is really a matter of does it wind up in a box or is it highlighted. Those are probably the two choices in

my mind. Dr. Temple, help us.

DR. TEMPLE: Well, I would say, not to try to preempt the discussion, it at least gets a black box.

DR. PINE: Why do you say that?

DR. TEMPLE: That is the least because the only data we have says the rate is something like 1/1000. It is life-threatening. Everybody has to know about this and we don't know the rate. It could be 1/300; it could be worse. I have discussed this with Tom and I am virtually certain that would be what we would do.

There are two other things to do though that you need to think about and address for us. One is whether it should be in some form or another recommended as not first-line therapy or think about other things first. There are various levels of subtlety in how to do it. We also are going to ask you whether we should ask for more data before we say yes. But maybe you think we are just wacky about the black box. That is all right, feel free to tell us.

DR. GOODMAN: Dr. Wang?

DR. WANG: I think there are several lines of argument that all point towards at least a black box. I mean, Lamictal sets the standard. If you are willing to put a black box for one Stevens-Johnson death out of 2000, here our best estimate is about 1/1000. The fact that, you know, with Lamictal the case was a fatal one doesn't really hold much weight. I mean, there are black box warnings for suicidality even though none of the cases were fatal. So, the fact that this one case didn't die is just fortunate I think.

DR. GOODMAN: I am sorry to interrupt, but the big difference there is we also didn't have efficacy, or at least very much efficacy.

DR. WANG: Granted. I think this whole issue of should this, on efficacy grounds, be a second-line treatment again pushes you. There appears to be less of a downside in putting something like a black box because if that de facto has the effect of causing it to be used second after failing a stimulant, then maybe that is, on

efficacy grounds, also justified.

DR. TEMPLE: I have to say we would be very uncomfortable without a direct comparison asserting--I mean, even though everybody loves this measurement and everything, we would be very uncomfortable asserting that it is second line because it is not as good, without direct comparisons. You can come back and say why don't you ask for direct comparisons all the time. That is another story.

DR. REESE: Dr. Rappley?

DR. RAPPLEY: Have we rendered an opinion about whether or not this is acceptably safe? I think in some ways we have taken a jump here and talked about what kind of labeling.

Also, something you said made me think the black box label, or whatever warning is on the label is not related to efficacy and that is not a risk-benefit judgment. That is just a statement of risk. Am I correct?

DR. PINE: The way it was discussed yesterday, and it would be nice to hear that again,

in what makes a black box it was a risk-benefit consideration and efficacy does go into the consideration, at least the way it was discussed yesterday.

DR. RAPPLEY: So, approval for use in children I see as weighed risk and benefit.

DR. TEMPLE: The decision to include a box has something to do with what the drug is for. If there were only one treatment for this and it was considered urgent to treat it, I don't know whether you would put a black box in. We don't box most anti-cancer drugs, but they are all lethal in one degree or another, because that is an expected part of the deal. So, what it is for and what it does has at least something to do with it. So, there are several other classes of drugs that work; you have choices; and here is one particular liability. But feel free to tell me I am all wet.

DR. GOODMAN: Let me stay with Dr. Rappley's comment. I didn't mean to short-circuit the discussion. I was offering my opinion but you are welcome to express the opinion if you feel,

based upon the dermatological issues, it is not reasonably safe.

DR. RAPPLEY: The way I am thinking about this is I understand that there is a particular metabolism of this medication in children and we have one case of Stevens-Johnson, perhaps 1/1000. We have plausibility that this medication can be linked to this serious condition. My understanding of under-reporting is that it is significantly under-reported and it is more likely to be common and I am reflecting comments from Dr. Bigby that we will find it associated in the future, and my faith in postmarketing studies is somewhat small.

So, given those things, I think that children are at risk for serious side effects with this medication and, if you ask me to do the cost benefit analysis, I think it is not adequately balanced by what we have to offer in bringing this to treatment of children for ADHD.

DR. GOODMAN: I would like to hear if others would share that point of view.

DR. REESE: Dr. Malone?

DR. MALONE: I think I partly share that point of view. I don't think it is safe enough to recommend it as a first-line treatment, especially when we have a number of effective, well-known first-line treatments--with the data that we have right now. It may turn out that this isn't going to be an issue but I think with the data that we have now it is hard to recommend as a first-line treatment something that could have such a dangerous side effect.

DR. REESE: Dr. Laughren?

DR. LAUGHREN: I just want to come back to a point that Dr. Temple was making earlier about what acceptably safe means. Part of what is inherent in that concept is having enough information to make a judgment about safety so I really want to make sure that you consider the full range of options. You might, looking at what you have, decide that you don't have enough information to make a judgment about safety but if you are going down that path, then tell us what more information you would like to see. But I just want

to make sure you consider the full range of options other than, you know, black boxes and whatever.

DR. REESE: Dr. Bigby and then Dr. Robinson.

DR. BIGBY: I actually enjoyed the comment at the end of the table here because I don't know if you figured this out but I like to try to make things simple. You know, thinking about it that way does actually make it simpler. The statement about we don't have enough information to say that it is safe, I would actually say it the other way and that is that we have reason to worry but we don't actually have enough data to say it is not safe.

DR. REESE: Dr. Leon?

DR. LEON: Well, I am concerned about a couple of comments I have heard in the last 10 or 15 minutes. Dr. Pine said right now it is just a judgment. Without putting words in his mouth, I think we are basing this without enough data. Dr. Bigby is predicting that once this is used widely we will see more Stevens-Johnson; Dr. Temple is

saying we need more data and suggesting we should look at more data. I don't feel comfortable saying it is safe until we have more data. There is at least one ongoing study. When are those results going to be in? There are 303 children, if I am correct, being followed right now. It is certainly worth waiting for them, and that is still a very small number.

DR. BIGBY: But those children aren't going to help you with the issue that you have.

DR. LEON: That is a good point, yes. But in my opinion we just have inadequate data. In the first 1000 there was a case. Is the next 1000 going to have 20 cases or zero cases? I don't think we can guess yet.

DR. REESE: Dr. Robinson?

DR. ROBINSON: Actually, it is interesting, what Andy is saying. I guess my question is, okay, we have 1/1000, how many more kids do we have to do to where we really say the estimate really changed dramatically, either going down or going up, that would be clinically

meaningful either down or up? Are we talking about having another 1000 kids? Another 10,000 kids? Because we are dealing with what seems to be a rare event with all drugs. So, that is the question. It is always good to say we would like more data but is that in the actual realm of doability?

DR. LAUGHREN: Actually, you can figure out how many patients you need to follow to cap the risk at whatever level you want to be comfortable with. We have this rule of 3 which, you know, estimates the upper bound of the confidence interval for the finding of no cases. For example, if you wanted to be comfortable with a level of 1/1000 you would have to follow 3000 for whatever period of time was of interest. If you found no cases, that would cap the risk at 1/1000. So, you can use that method to calculate how many patients you would have to look at, at the doses of interest and for the time period of interest, with the finding of no events that would cap the risk. Now, if you wanted to cap the risk at somewhere near the background rate, that is not a doable experiment

but you could at least figure out, say, with 3000 that the risk is no greater than 1/1000 if you found no cases.

DR. REESE: Dr. Pine?

DR. PINE: I guess two things. I want to bring up one point that we haven't spent much time talking about, and that is kind of the need for more treatments in ADHD. You know, the important thing to remember is, yes, clearly stimulants are effective. No question, and they are good treatments and there are other treatments around. Again, no question. But even when medications are effective the amount of improvement that you get even when treatments work well is often not necessarily what you want, and there are not nearly enough treatments available for kids with ADHD. You know, I think it is hard to say where this is going to fit in and I would totally second what Dr. Temple said, you know, to base a decision on limited use on efficacy would not be a good thing to do because it is a yes/no question. The medication clearly works. And, I am uneasy about

withholding treatment that could be potentially efficacious given the availability of treatments, such as they are, for ADHD. So, that is the first thing. I don't think we have spent enough time recognizing that fact, that there are clearly needs for other treatments. Number one.

Number two, thinking about that on the one hand, with capping the risk on the other hand, just personally, off the top of my head, I would be much more comfortable if we could cap the risk at 1/1000. I would feel much more comfortable about making a statement or decision or conclusion about whatever the word--what is the word, relatively safe?--acceptably safe. If I knew that a good estimate of the risk was 1/1000 I would feel a lot better. If you are saying that 3000 cases treated for two weeks openly and we see no cases would answer that question, I would feel a heck of a lot better.

DR. TEMPLE: That is our rule of 3, and I am sure Dr. Leon can explain why it is not quite right but it has been considered close enough.

Just another way to look at this, suppose you thought that the risk could be as great as 1/500--I mean, the data we have now has a confidence interval and it probably goes down to 1/300 or something like that, where would you be comfortable? You just said 1/1000 properly labeled and everybody knowing it would probably be okay. But I think it is important to discuss that.

DR. PINE: One in 950.

DR. REESE: Dr. Pfeffer?

DR. PFEFFER: I think there are several other considerations. I certainly agree that if we can enlarge our treatment spectrum for this disorder it would be wonderful. But I also think that we in a way have concern about the potential risks in this case without sufficient data, and I am thinking also about what happens in the real world once a drug is approved. Many of the children with this disorder are treated with multiple medications, unfortunately, and I would wonder about what drugs might have potential for cross-reactivity that might increase the risk for

these children. And, I tend to think that we have a disorder that is severe, there is no doubt. We have carefully tried to develop approaches to treat these children and perhaps a careful approach is to ask for more data and to sort of place that in abeyance for the time being until we can answer this question with a little bit more assuredness. It just raises a new issue because we did talk about some medications, one of which I think is commonly used, which could have cross-reactivity.

DR. GOODMAN: Let me clarify. We have 1/1000 and there was an estimate of--what was it?--5 percent of cases of Stevens-Johnson lead to mortality?

DR. BIGBY: Yes.

DR. GOODMAN: Let's start with that just as a figure. How many open cases would you need to treat, for what period of time, in order to gather those data with some degree of confidence?

DR. TEMPLE: I don't think you could imagine getting good mortality data--

DR. GOODMAN: No, I am not talking about

mortality data.

DR. TEMPLE: Well, to take a simple task, as Tom said, if you wanted reasonable reassurance that it was not greater than 1/1000, if you had data on 3000 people and no cases that would provide that. I mean, the tension we have had is here is this one case in 1000. Here are 30,000 people treated, no cases. Is this just some wild, weird fluke or is that close to the true rate? You might even decide--I mean, you did say even if that is the true rate, that might be okay. Maybe you would make it second line or do something else. That might be okay. But at the moment, one of the reasons this was brought to you is we don't know what the rate is. We don't have enough data to know what the rate is and it could be rather high or maybe it is really low and this is just a fluke and that is our uncertainty.

DR. PINE: Speaking only for myself, that is what I would want to know and I would be comfortable with that, but until I know that it is going to be hard for me to make a decision.

DR. REESE: Dr. Rappley?

DR. RAPPLEY: I could ask it another way. Is anybody comfortable with the amount of data that we currently have? Then we could move to discussing what additional data we need if there is further discussion on that. I don't mean to push.

DR. GOODMAN: No, that is good.

DR. TEMPLE: Just one thing, as you discuss that I think it is important to think of enough data for everybody, enough data for a fairly scary statement that says this is only for people who haven't responded well to other things, not that we have data on that but, I mean, there are a number of things to think about as you discuss this.

DR. PINE: Again, related to the discussion we have had I don't think the questions are really about efficacy or what the niche is going to be so, personally, I would care less about who receives the medication in terms of what narrow type of condition they have, and I would be more concerned with capping the risk estimate. Based on

what Dr. Bigby said, it seems to me 3000 patients treated for a month openly would be what you would want to do.

DR. GOODMAN: We are not finished with this obviously. I would like to move on to some of the other concerns we have and see if we can go through a list and perhaps even identify where we think that this medication might have some advantage, some possible niche.

In terms of cardiac issues, those were discussed at some length yesterday. I think in the context of stimulants it was decided that an individual who had known structural cardiac abnormalities should not be prescribed a stimulant. Would we be having similar concerns about this agent? In the data that I have seen there wasn't very much evidence for increases in cardiac parameters such as heart rate or blood pressure and, therefore, would it be in that context perhaps a safer alternative?

DR. REESE: Dr. Andreason?

DR. ANDREASON: I just wanted to add that

in the Provigil labeling already it warns against using modafinil in patients with hypertrophy and bicuspid aortic valve.

DR. GOODMAN: So, you would already put it in the same category with the stimulants?

DR. ANDREASON: Well, it kind of already is. It is already in labeling. Unless you felt that the data that was presented should remove that.

DR. GOODMAN: I don't see anyone saying yes.

DR. REESE: Could you come to the microphone and state your name? Thank you.

DR. HERSKOWITZ: Norman Herskowitz, medical officer in DMP. In the labeling, as I recall, it really discusses the limitation--I think this is the initial studies--to issues of mitral valve stenosis and regurge type of syndromes, but not to any other sorts of cardiac history. So, that is just for information sake.

DR. ANDREASON: I am pulling up that labeling for you; I am not as fast as I thought I

would be.

DR. HERSKOWITZ: It mentions some very subtle changes in blood pressure, but extremely subtle. In the adult studies there seemed to be a pattern of increase in anti-hypertensive use although no changes in mean blood pressure.

DR. ANDREASON: I have it. This is under cardiovascular system in the Provigil labeling. It says in clinical studies of Provigil signs and symptoms, including chest pain, palpitations, dyspnea and transient ischemic T-wave changes on ECG were observed in three subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that Provigil tablets not be used in patients with a history of left ventricular hypertrophy or in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome in previously receiving CNS stimulants. Such signs may include but are not limited to ischemic ECG changes, chest pain or arrhythmia.

DR. GOODMAN: And that is at a lower dose

than is being proposed.

DR. ANDREASON: Correct.

DR. REESE: Dr. Rappley?

DR. RAPPLEY: The discussion yesterday from Dr. John Moore who is a pediatric cardiologist on the Pediatric Advisory Committee and, Deborah, add to this if you can, we talked about how the increases in blood pressure and pulse were perhaps not clinically significant for children but statistically significant and, yet, the concern persists because of the idiopathic hypertrophic subaortic stenosis being a condition that really cannot be detected in the population until the serious adverse event occurs, and that it is plausible that increasing sympathetic tone could contribute to that in the same way that running track or becoming dehydrated does.

DR. GOODMAN: After Dr. Pine makes a comment I would like to take a ten-minute break before we come back for further discussion and vote on the second question. I need a few minutes to deliberate. Dr. Pine?

DR. PINE: I guess with a lot of these secondary adverse effects--the cardiac effects, the psychiatric sequelae, the growth effects--for some of the same reasons that people were uncomfortable making statements about comparative efficacy, I would be uncomfortable making statements about comparative adversity unless there have been head-to-head trials, which there haven't been. You know, my take from looking at all the other data, besides the dermatologic data, I am slightly concerned with the psychiatric adverse effects, no more concerned here than the discussions yesterday, and I just think it is probably not fair, given the data, to make statements that this is better or not better than any other agent unless they have been compared head-to-head. I think it is, you know, is it safe enough or not for all of these secondary issues and, again, in my mind it seems safe enough, whatever that means.

DR. GOODMAN: I would agree. Let's take a ten-minute break.

[Brief recess]

DR. GOODMAN: It seems to me that a lot is hinging on one case and I still haven't decided which way I want to go based upon that pivot point. So, let me just go back to that case for a moment. First I would like to hear from Dr. Bigby. I think I have already heard, but I need him to repeat, that there was definitely a case of SJS but I would like to hear again his opinion on the association between the drug and that case of Stevens-Johnson syndrome.

DR. BIGBY: My opinion about that reported case is that it is probably a case of Stevens-Johnson syndrome related to the drug. Now, that doesn't mean that it is definitely related to the drug. And, I think that the difficulty would be for anybody to say with any certainty that it is not drug related. But, you know, am I absolutely certain that it was due to the drug? No. But I wouldn't want to be put in the position to argue that it is not drug related. That is the problem we have.

DR. GOODMAN: I understand that the

investigator who treated that subject is here. Could that person identify himself or herself? Would you mind coming forward and just describing your impressions of the case?

DR. REESE: Could you please be sure to identify yourself, sir?

DR. BELNOR: I am Samuel Belnor, a pediatric neurologist and I was the principal investigator on this case that was a 7 year-old Asian boy who is perhaps the most compelling case for Stevens-Johnson. My impression on this patient--and then I will go into detail, but my impression was that the most likely diagnosis was erythema multiforme, possibly Stevens-Johnson. The most likely etiology was a viral infection, possibly drug related.

The patient had shown improvement in the clinical symptoms of ADHD after one week on drug and was seen on the 14th day. On the 14th day the patient presented with fever of 101.9, a sore throat and feeling bad. I was out of town but the sub-investigator, a pediatrician, saw the patient.

The mother complained of two lesions on the leg which she thought were possibly a brown spider bite but there was no rash. The next day the sub-investigator put the patient on amoxicillin and did a rapid screen for strep. which was negative. The throat, he felt, looked like a viral throat infection. There was no exudative pharyngitis but papules in the throat. The patient was seen the next day by a pediatric group locally. The pediatric group saw typical lesions of Coxsackie B virus in the posterior pharynx and diagnosed this patient as having a Coxsackie B virus infection. The rash was over most of the areas of the body but it was more marked on the face and extremities. Also, they felt that the two lesions on the legs were the target lesions of erythema multiforme.

The patient did not develop any apparent--there were no lesions in the mouth at that time and no mucous membrane involvement. About six days later--I apologize, we have a real lack of data because the mother did not bring the patient back to us until four weeks after the rash

developed, in spite of being called on numerous occasions. She had a single family business and was the only employee and would not bring him back. He went to school many of these days. We told the family the day of the rash to stop the drug. The teacher recommended, on day 23, that she felt that he should go back on the drug because his behavior was much worse and the mother gave him one dose of the drug and nothing really changed much except that she felt that he was maybe pealing more and did not give any more.

No one saw the lesions in the mouth, other than the mother, and she thought that there were lesions in the mouth because he would not eat well. No physician see mucosal involvement. He did complain of burning when he urinated, which is a possibility.

The patient really felt quite good during this four-week period from the onset of the rash until we saw him next. He went to school about half the time. The mother was really unconcerned. When I saw him four weeks after the rash onset I

saw no lesions in the mouth. There was no evidence of any previous lesions in the mouth. He was happy; no stress. And, his skin was pealing. There was no evidence of any dermal involvement other than just some pealing of the skin, mainly on the extremities. There were no lesions in the posterior pharynx of the Coxsackie B virus.

If we had seen the patient earlier we obviously would have done a skin biopsy. We did a RAS test later to modafinil and to amoxicillin--of course, it is of limited value, but it did not show any positive reaction.

DR. GOODMAN: I would like comments on what you have just heard from either Dr. Rappley or Dr. Bigby. Does that help one way or the other in the diagnosis?

DR. BIGBY: Given the description, I don't think that anybody can say that that was not a case of SJS. You know, it would be nice to know if the patient had typical targets or not but I don't think you are going to get that described in this case.

DR. RAPPLEY: I guess for me it is the degree of uncertainty that we have at every point; it is sort of the added uncertainty that makes me uneasy; that makes me unwilling to say that it is just fine, let's go forward and treat everybody.

DR. GOODMAN: Can you repeat that?

DR. RAPPLEY: It is the degree of uncertainty that we have that makes it difficult for me to say that it is fine or perfectly acceptable to proceed with just having people make sure they report rashes.

DR. GOODMAN: Dr. Pine?

DR. PINE: I want to go back to the statement Dr. Temple made. You obviously seemed very taken with this when you said it is at least going to get a black box and we moved away from you fairly quickly. Could you just spell out your thinking, what made you react that way? I mean, I think it is more than just this one case or maybe it is just this one case but I would like to hear that.

DR. TEMPLE: Well, it goes without saying

that I have no credible, sensible view about whether this is a bona fide case or not. I am listening to people who do though. So, what we are seeing is that in something like 1000 people, but perhaps when you look at exposure it may be 700 or 800, you have one case that is at least statistically compatible with rates that are high enough to be worrisome, you know, down to one in a few hundred and up to whatever, and a condition that is very scary and is life-threatening. So, it all turns on believing the case. I mean, if this was dismissable I wouldn't have said that but everything I have heard up to now, both internally and even from the company, says that this is a plausible case.

So, when your best estimates of something very worrisome are in the neighborhood of 1/1000, you know, of it was agranulocytosis or something we are accustomed to taking full note of those. That is really all I meant.

DR. PINE: Yes, that is helpful. Thanks.

DR. GOODMAN: Dr. Mehta?

DR. MEHTA: Actually, I have two questions of the investigator. One is was the patient hospitalized? And, what surface area of the body was affected by Stevens-Johnson syndrome?

DR. BELNOR: I am sorry, will you repeat the first question?

DR. MEHTA: Was the patient hospitalized?

DR. BELNOR: No. Although most of the areas of the body were involved, the total surface area of the body involved, according to the mother's history and the pediatrician that saw him and our examination when he came back, was less than 10 percent.

DR. MEHTA: Can I ask Dr. Bigby a question?

DR. GOODMAN: Sure, go ahead, Dr. Mehta.

DR. MEHTA: What percentage of Stevens-Johnson syndrome patients would be hospitalized?

DR. BIGBY: Excellent question to which I do not know the answer.

DR. GOODMAN: Ms. Bronstein?

MS. BRONSTEIN: I think there is another signal we can't forget and that is the adult population on the low dose having three cases in a little over a million, which is two cases more in a million than the general population on the same drug. So, you know, even if there is some question there is also some other linking stuff, at least in my mind.

DR. GOODMAN: Dr. Laughren?

DR. LAUGHREN: Could we get some clarity, maybe from Dr. Bigby, on what the background rate of Stevens-Johnson is? Then, what the reporting rate is in this experience with this drug in adults?

DR. BIGBY: If you look at sort of population-based studies the estimate is one case in a million or 500,000. If you look at the case-control study that was done in Germany, Italy and France where they sort of specifically tried to identify all of the cases over a period of time and they took detailed drug histories from the patients and they limited the definition to SJS and TEN the

way I defined it in my talk, it was in the order of 1/100,000 to 1/400,000.

DR. LAUGHREN: So, it sounds like it varies anywhere from 1/100,000 to 1/million. Do we have clarity on what the reporting rate is for those three or four cases in adults? Maybe the company would know that.

DR. CIVIL: Yes, for the person taking the transcript, my name is Rich Civil, C-i-v-i-l. Our reporting rate for events coded as SJS and TEN, the number of cases we have has been discussed. There are five. Each of them can be looked at individually and, indeed, the discussions up to this point have already excluded largely from consideration one of the cases, that being the patient with subarachnoid hemorrhage who developed the cutaneous skin reaction in association with the apparent initiation of treatment we phenytoin and phenobarbital. Subtracting that case out, we have four cases in approximately 750,000 adult patient-treatment years of exposure.

Given the described hazard profile which

suggests a greater risk in the first four weeks perhaps, we recognize that a better denominator for that exposure would be patients rather than patient-treatment years. Based on what we have estimated as an average treatment duration of approximately 2.5 months on average in the postmarketing environment, we would then calculate that the 750,000 patient-treatment years translate to the rough equivalent, based on IMS estimates and survey data, of approximately three million patients treated.

DR. LAUGHREN: So, the reporting rate with that denominator is roughly one per million. So, there you have it. I mean, you have a reporting rate of one in a million; background rate somewhat less than that.

DR. TEMPLE: Well, that doesn't take in the under-reporting.

DR. LAUGHREN: Right, but we usually compare reporting rates to background rate, understanding that there is under-reporting. We generally take some comfort if the reporting rate

is well below the estimated background rate.

DR. PINE: I guess my question is what is the downside of capping it at 1/1000 by studying 3000 more patients? As far as I can hear, the only downside is that we are going to delay putting the treatment on the market for six months or a year, which seems like a risk worth taking if we really want to be sure that, you know, 1/1000 is really the risk of Stevens-Johnson. I mean, that seems like a fairly fair trade, you know, to be sure that the rate is really no higher than 1/1000 and we delay approving a treatment for however long that takes, six months or a year. DR. LAUGHREN: That is precisely what we are asking the committee.

DR. TEMPLE: Right, and people have to weigh the cost of the delay and the consequences of not doing that.

DR .MALONE: Most of the talk has focused on the one Stevens-Johnson. What about the other case? I didn't quite understand the case where there was urticaria. Was that thought to be drug related or a signal of anything else related to

serious skin reactions?

DR. BIGBY: I think that that case is less than 50 percent likely to be drug related.

DR. GOODMAN: If this were a new molecular entity with no prior marketing experience and I was presented with these data, with the degree of uncertainty that we are all facing, I would say we needed additional data, for sure. And, I think one of the reasons that I have been on the fence in the last hour or so is because it is an agent that has been out there for a long period of time. But, given the fact that it is at a higher dose and it is going to be given to a population that metabolizes it differently, perhaps I should be taking it more as if it were new rather than a different indication for the same compound in the same population.

So, I would have to say I am leaning at this point to recommend additional safety testing. I don't feel, as I re-read this question, that modafinil has been shown to be acceptably safe given the doubts that we have in our minds. If it

turns out to be 2/1000 I think we would all regret the decision to go forward. I don't want to do that experiment in the postmarketing arena.

I think, that said, if we are to recommend the studies--hopefully, the FDA would be the ones to really design this--that we don't set the bar too high. I don't want to be disingenuous. I think that this is a drug that we all agree is efficacious. There may be certain advantages over existing compounds. Some of those are yet to be proven. I would like to see an opportunity for the company to come back with those additional data that would give us an extra degree of assurance that this case was a fluke, and that could exactly be what it was.

DR. LAUGHREN: I think it is important to be clear about what level of comfort we could gather from the study that I proposed earlier. The most you would be able to do is to cap the risk at 1/1000. So, even if you did that and you were comfortable with that as a cap, I think the drug would still have fairly strong labeling. I just

want to be clear about that. It is not going to make the problem go away.

DR. PINE: Related to that, there probably would be some discussion about, you know, let's say you could do a larger study and cap the risk even lower. You know, maybe people would want to do that. There could be some discussion about that. I think that is probably going a little far based on the data we have right now. I think the question is, is it safe enough or not and that is kind of what we are debating.

DR. GOODMAN: Dr. Wang?

DR. WANG: I am a little bit less sanguine. You feel that with a study of another 1000 patients maybe you will cap it at 1/2000. It quantitatively gives you reassurance; it won't qualitatively necessarily give you maybe the reassurance we are looking for. One thing in favor of additional studies is an active comparator, a study that actually could maybe sort out sort of where in the armamentarium this might fit in.

DR. GOODMAN: Dr. Bigby?

DR. BIGBY: Somebody has to clarify to me then what is the black box labeling for Lamictal. If they have a rate of 8/1000 in children what does the label say?

DR. ANDREASON: Let me put it up.

DR. PINE: The other thing to remember about the labeling for Lamictal is that it is for Lennox Gasteau syndrome so it is a different disorder fundamentally.

DR. TEMPLE: And for which I believe there is no other treatment.

DR. PINE: There is no other treatment, that is right.

DR. TEMPLE: It makes a difference. I am confident if there were no other treatment here our discussion would be different.

[Slide]

DR. ANDREASON: Here is the lamotrigine black box, or at least the part that has the data and the warning up front. This is for Lennox Gasteau in kids and then adjunctive therapy for epilepsy in adults and bipolar in adults.

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: Well, I am sure you are going to want people to discuss what you just said but I just want to throw one other thing into the mix, and that is, suppose the company did a study showing definitively the way I want it shown that it really did work in people who failed on other therapy--a properly designed study, not that hard to do if it really does work in that setting, would that make any difference in all this?

DR. GOODMAN: It would make a difference. It would definitely wind up with a black box.

DR. PINE: I don't think it is an either/or though. I would want to cap the risk.

DR. TEMPLE: Well, that is what I am asking. What you have just been discussing is capping the risk before it gains approval for this use. What I am asking is if, before doing that, they knew that it unequivocally works in people who failed on other therapy would that make you want to make it available even before you capped the risk, with an appropriate box, or not?

DR. PINE: You know, that is a theoretical debate. I would have to see how well does it work; does it really beat a stimulant head-to-head; who are these people--

DR. TEMPLE: That is the test. It would have to beat the drug they supposedly failed on, presumably a stimulant, in a randomized trial and it would have to beat it.

DR. PINE: That would be great. I mean, I can't tell you that I would definitely say forget about the risk if you show me that, but it definitely changes the discussion we are having right now quite appreciably.

DR. GOODMAN: I would echo Dr. Wang's point earlier that not having the comparative data I think is a weakness of this application.

DR. PINE: But, personally, I don't think you have to have that. I mean, I think if it worked just the way it does work and you knew that the risk was 1/1000, again just speaking for myself, I would be comfortable with that.

DR. TEMPLE: No, I just meant whether you

could truncate further characterization of the risk if you knew that thing about it. Maybe that is such a hard study nobody is even interested but you don't know until you ask.

DR. GOODMAN: Dr. Bigby, has your question been answered?

DR. BIGBY: Yes.

DR. REESE: Dr. Malone?

DR. MALONE: If you did such a study, then would the label reflect that it was approved for the treatment of patients who failed other treatments or would it not include that in the label?

DR. TEMPLE: Excellent question. With clozapine where we had those data the labeling said you should have failed on other therapy because the 1.5 percent rate of agranulocytosis was considered unacceptable in a first-line population. So, if there were no further characterization of risk you might very well say that it is for people who failed other therapy, and maybe you wouldn't have to wait for the further characterization of risk.

If the risk were then further characterized and everybody was comfortable, maybe then we would feel it could just be thrown into the mix and they would have this particular piece of information.

DR. MALONE: How well do post-approval registries help resolve a question like this because it won't be that easily resolved? And, how would you do that?

DR. TEMPLE: Yes, that is a hard question. There are probably people better able to answer. The most successful registries are ones where you are controlling distribution so, for example, the clozapine registry, in my view, is a huge success because you can't get the drug without going to the right pharmacies and your name goes in it, and one of the purposes of it is to keep people who have already gotten agranulocytosis from ever getting the drug again and, as near as we can tell, it has been very, very successful and there have been analyses, but that is because you have to sign up to get the drug.

Registries ordinarily in many other cases

are voluntary and whether people stick to them or not is uncertain, and they have varying degrees of success. We would have to get some people who know more about it than I do to answer that though.

DR. MALONE: Currently, with stimulants you almost have to see a patient fairly regularly because you have to keep writing the prescription. Could a registry be developed by requiring a script from a doctor? At least they could ask if they had a rash.

DR. TEMPLE: Well, any system that limits distribution--first of all, it is very difficult if the drug is already available in another form. Second, they are a lot of trouble. I mean, we do those things for drugs we are really worried about. There is one being set up for Accutane that is more rigorous than before; thalidomide--I mean, those are the things we are talking about. You don't do them lightly because there is actually some evidence that they interfere with use. We have distribution system for a drug called dofetilide that is used to maintain normal sinus rhythm and a

study, I guess out of Duke, showed that people are using solatol or quinidine instead. Well, that was not what we had in mind. So, you have to fit it into the system and it has to work out.

DR. GOODMAN: Dr. Malone, by this line of questioning, are you suggesting that our target would be to vote in favor of the compound but to put in place a rigorous registry program to monitor for rashes, particularly Stevens-Johnson?

DR. MALONE: No, I wasn't trying to suggest that. I don't think it is going to be easy to answer how often a rare event occurs if you do more patients. So, I think in the end you are going to have to have a longer way of answering that question. I wasn't trying to suggest that you would approve it and then handle it that way.

DR. GOODMAN: Any members of the committee that would like to argue in favor of this being shown acceptably safe, and we are focusing on the dermatological complications?

[No response]

I would like to give a representative of

the company a chance to argue that point before we take a vote.

DR. RUSSELL: I would just like to ask Neil Shear to give his opinion on the risk of Stevens-Johnson.

DR. SHEAR: Well, I guess I can perhaps add strength to your difficulty. The question of this single case is exactly the way I would have explained it, that there was a single case that was sort of convincing. It didn't meet a definition of Stevens-Johnson because the body surface area of epidermal detachment was not high enough. It would probably meet a definition of erythema multiforme major, and it probably is post viral.

The other issue you can look at is it is not 1/1000 because it was 10/10,000--it was one and that one could easily be zero and that one could be two. So, in terms of it perhaps being a fluke, I think there is some strength to that argument. Then trying to do the balance that you are talking about, I think, you know, you have raised various possibilities. I don't feel it is up to me to tell

you what to do on that. But keeping track of reactions has been done before for other drugs.

I would also say that because of its already accumulated experience, the pediatric dose notwithstanding, this is not Lamictal. This is not a drug that had started right from the beginning--Lamictal, when it was started in England out of Burroughs Wellcome, was causing problems immediately and continued to cause issues. Now, some of those are probably over-ascertainment because people were jumping on the bandwagon in terms of diagnosis but, still, it is a drug that has a very different risk and I think that has been managed over the years, actually many years now. Here is a drug that was on the market. It is not a new chemical entity but is being used in a broader population in children so you have the balance there.

What I have seen so far has not convinced me. I think where I would differ from Dr. Bigby is that I don't feel that I can absolutely--and I don't think he said absolutely, but I don't know if

I can really confidently say that there are going to be cases of Stevens-Johnson/TEN with this. I just don't see that based on the exposures we have but that is, again, just personal after looking at many of these drugs for many years. If you look at dilantin, if you look at sulfonamide, they were recognized in the '30s. When they first came on the market it was clear that these drugs were causing these kinds of problems right away.

I do want to make one more comment since I have the microphone for a second, the sulfonamide allergy story--for the severe reactions to sulfonamide it is the aromatic amine at the end of the molecule and not the sulfonamide moiety that is considered to be responsible. There is certainly no evidence to the contrary and the only evidence that exists on a metabolic basis is that the aromatic amine is hydrolyzed to a hydroxylamine which goes on to become a nitroso, which is a P450 pathway through 2C19, and that is what appears to lead in vivo and in vivo to toxicity.

DR. PINE: I would like to ask you a

question about your statement about where you would disagree with Dr. Bigby. How confidently would you assert that you doubt that we would see additional cases? I understand that you said that there is not a lot of evidence to support that.

DR. SHEAR: Well, I guess what I would do is look at the cases that exist. What is real? What am I comfortable with? We do see that there are some cases in the adult literature. It is hard to tell but, you know, we do have some numbers that are low, like background, and they are in the 1/100,000 to 1/million type of range. Though adults don't usually get Stevens-Johnson syndrome that often, we do see it. We do see people come in; they have no drug and they get a real Stevens-Johnson syndrome. So, that is probably out there. The pediatric exposures of at least 30,000 children--Dr. Andreason showed the numbers for people who were getting the drug through various programs, and they had none in 30,000 exposures. Again, if this case was rock-solid Stevens-Johnson, which it doesn't appear to really

be by the usual case definitions that we use nowadays, but if it is erythema multiforme major, which is something that kids do get and something that suggests viral from what we heard about the case, the more you dig into this the more I am getting more comfortable that it isn't. And, until I had a chance to actually talk to the investigator I don't think I would have been saying this, but looking at it in its totality and trying to balance it against the other known hard-core data, that is what makes me more comfortable and I think I have had that information maybe hours longer than Dr. Bigby, but not much more, and I think you do get more comfortable, and we sat down as a group of experts to talk about it and we did become more and more comfortable where that probably fit.

DR. REESE: Dr. Bigby?

DR. BIGBY: Do you have a response to the question that was asked about what percentage of patients with Stevens-Johnson syndrome get admitted to the hospital?

DR. SHEAR: Yes, your answer was a good

answer; it is a good question. I mean, we do sometimes see people who come in who we think have Stevens-Johnson admitted to the emergency departments, but I would say that if they actually had some real epidermal detachment they would be admitted not only to hospital but probably to a burn unit. I mean, we are talking about some pretty sick people and if you see a kid with truly Stevens-Johnson syndrome, well, you are not going to send them home. Unless you want to, you know, not only potentially kill the child but end your career, you are not going to do that. This is a serious event and it is easy to recognized. This is not a subtle diagnosis really. I mean, these people have mucosal blistering that is not only horribly painful but is hemorrhagic, and that is not what we saw in this case and, again, we have not seen any reports in the larger pediatric population or the postmarketing surveillance.

DR. GOODMAN: Further discussion? Dr. Mehta?

DR. MEHTA: I have worked in the drug

industry for about 40 years and I must say that I have worked with a lot of different drugs and I have seen during clinical studies about 20 patients with toxic epidermal necrolysis or Stevens-Johnson. I don't recall a single patient not being hospitalized. Every single patient is hospitalized. It is such a serious disease because mortality now is about 5-15 percent. Ten or 20 years ago it used to be 50 percent. So, every patient was hospitalized.

DR. GOODMAN: Dr. Rappley, do you have a comment?

DR. RAPPLEY: All day we have dealt with the uncertainty before us but now we hear a lot of confidence that it is not Stevens-Johnson. I, myself, am not changing my view on this.

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: Well, let me offer a suggestion or a question. My assumption is that to the extent confidence that this case really represented Stevens-Johnson, you would be more comfortable with going directly to approval perhaps

with language in the labeling, and I don't think we are going to be able to fully do that here. So, let us tell you--you know, we might telephone you or something, but we will look more at this. We have experts around even though none of us personally knows about it. If the case starts to look very weak, that is going to change things and i think we understand what you think about that. But if the case stays reasonable strong, not 100 percent but reasonably strong then I think we have heard your advice.

DR. GOODMAN: I find that acceptable. I would like to call the vote on the question based upon what we know now.

DR. RAPPLEY: Will you clarify what it is that we are voting on?

DR. GOODMAN: Has modafinil been shown to be acceptably safe in the treatment of attention deficit hyperactivity disorder in children and adolescents? You have a comment, Dr. Andreason?

DR. ANDREASON: Yes, Dr. Luke had a question about the case report versus the report

given by the investigator.

DR. LUKE: Yes, in the original written case report it stated that it covered the entire body. It was described very differently from how the investigator describes it today. I think that contributed somewhat to the relative uncertainty that we are now hearing within the last half hour or so. So, the question is what is the real story, was it the written report provided by the sponsor or is it the investigator's testimony given now at today's meeting?

DR. BELNOR: I don't think we have changed the story. The implication was that it was on all areas of the body but it didn't cover every area of the body completely. It was less than 10 percent of the total body surface area. It was on the trunk, the face, the extremities and the back.

DR. LUKE: So, you are saying the pealing is less than 10 percent but perhaps the rash itself--

DR. BELNOR: No, the rash. The rash was around 10 percent by the history that we obtained

from the pediatrician.

DR. LUKE: Oh, so it is by history. You did not yourself observe this?

DR. BELNOR: No, the peeling looked like it was obviously less than 10 percent when we saw the patient.

DR. LUKE: So, then there is still some doubt. It is really hard for a dermatologist, and I know other dermatologists in the room can attest to it, to make an assessment from hearing a story, especially if it is not carefully written up. Photographs are often helpful and biopsies are helpful but, again, it is lack of information that adds to uncertainty.

DR. GOODMAN: Let's go ahead with the vote. I am going to start with Dr. Bigby.

DR. BIGBY: So, is this a yes or no answer?

DR. GOODMAN: Or abstain.

DR. BIGBY: I would say yes, it is acceptably safe.

DR. GOODMAN: And explain your reason.

DR. BIGBY: You know, I think that this is an instance where we are being asked to make a decision on the basis of a single case that is probable but not definite. I mean, I have concern that when the drug is more widely used over a longer period of time you are going to see cases of SJS but you see that with lots of other drugs that are already marketed.

DR. GOODMAN: Before I go on with the vote, I actually expected a different response and I am assuming others did too. So, maybe there is room for further discussion, given the opinion you just rendered, before we go on with the vote. Does that change anybody's mind around the table?

MS. BRONSTEIN: I have one question of the investigator. It was my impression that you did not see this patient yourself until four weeks after the very final time the mom brought the child in. Is that correct?

DR. BELNOR: The mother refused to bring the child back in from the second visit until the last visit.

MS. BRONSTEIN: My question is when did you lay eyes on the patient.

DR. BELNOR: I saw the patient at the first visit.

MS. BRONSTEIN: Before the rash?

DR. BELNOR: Before the rash.

MS. BRONSTEIN: And did you see the patient on the last visit?

DR. BELNOR: Yes.

MS. BRONSTEIN: But not when the rash was in its fullest--

DR. BELNOR: No, none of the investigators saw the patient when the rash was present. We told the referring doctor to stop the medicine and send the patient to us for a biopsy.

MS. BRONSTEIN: And who did the write-up of the patient that was received?

DR. BELNOR: I did.

MS. BRONSTEIN: The first write-up that was received to the company?

DR. BELNOR: I did most of the write-ups. I don't know. There are a lot of errors in the

history.

MS. BRONSTEIN: Thank you.

DR. GOODMAN: Do you have any further comments?

MS. BRONSTEIN: I am left with a lot of questions and a lot of lack of confidence, and I feel like erring on the side of conservatism, either longer testing or saying no but as the consumer representative I feel like the public needs to be protected and we have a lot of questions here. As a working mom, I really can relate to this mom not bringing the kid in; I did it myself. And, I don't know that you are going to get good anecdotal reporting. I also don't have a lot of confidence in non-dermatologists reading rashes. So, that is where I am with all this.

DR. GOODMAN: Dr. Wells?

DR. WELLS: While it may be true that the case for lack of safety has not been made, it is also true that the case for safety has not been sufficiently made, and I think that is what we have to have in order to make a statement that it is

adequately safe and I am not there.

DR. GOODMAN: Dr. Pfeffer?

DR. PFEFFER: Am I voting or making a comment?

DR. GOODMAN: You are just making a comment.

DR. PFEFFER: I wanted to ask, I just began to remember, isn't it true, Dr. Bigby, that this problem, Stevens-Johnson for example, doesn't always appear on the entire body simultaneously? Isn't there a course that goes from head to foot? So, I was wondering about this case. How frequently did the pediatrician see the child once the rash occurred?

DR. BIGBY: So, Stevens-Johnson does normally evolve over a period of several days, and it is true that it is not full-blown at its onset. People can continue to get lesions over several days. I would say in the majority of cases you start getting new areas of involvement after about a week or so.

DR. GOODMAN: Dr. Robinson?

DR. ROBINSON: Well, I think it is very striking that the one case that we are debating about came in the context of somebody who was in a controlled trial. Even in a controlled trial, which wasn't designed to look at this issue, we are in the situation where experts can debate back and forth, and I think that says that if we approve the drug and say there is going to be postmarketing we would not get data that was really usable because even in a controlled trial we are debating. I think that argues for us getting a study design to look at this specifically so if somebody has a suspected case of it the proper information is obtained, like photographs and expert dermatologic consultation so that we can actually say what is an estimate. It is just striking that even in this sort of controlled trial we are not getting the information we need and I think that argues for a specific study.

DR. GOODMAN: Dr. Armenteros?

DR. ARMENTEROS: I also have a concern that I am not so sure that even a controlled trial

moving forward from this point would still resolve our doubts. I am concerned about that.

DR. GOODMAN: Dr. Andreason?

DR. ANDREASON: I suppose for something that is as rare as Stevens-Johnson or, say, something like acute liver failure you don't even need a controlled because the historical control is so rare that if you pick up a case in an open-label trial of, say, 3000 patients that is significant. So, that would be an acceptable design to look at something like this.

DR. GOODMAN: Let's start with the vote again, and this time I will begin with myself. I am going to vote no. I have been persuaded by my colleagues around the table and my comfort level is not sufficient that this has been shown to be acceptably safe. I don't know what to make exactly of that one case and, frankly, I don't think we are ever going to be sure. It certainly raises a sufficient number of doubts about a serious adverse event that should not have occurred even at the rate of 1/1000 or less that we saw in this trial.

Perhaps the other factor that has led to my decision is the absence of other strong, convincing reasons to consider this drug having advantages in other areas of safety or tolerability or efficacy so I am not willing to find the risk acceptable of going forward without additional data that would rest some of my concerns about the dermatological reactions. Now we can go back to Dr. Bigby.

DR. BIGBY: I voted.

DR. RAPPLEY: I do not think it is acceptably safe and I think you all have articulated my feelings.

DR. WANG: I think it is just unknown. Can I abstain until we have more information? I mean, it could be everything from this things shouldn't be approvable if this is a real signal to there is no warning needed at all if this isn't the case. We don't even know what to make of this case. There is no temporal or inter-rater reliability even within this meeting.

DR. GOODMAN: Dr. Laughren?

DR. LAUGHREN: Actually, I don't understand an abstention in this situation. I mean, we are asking you if you feel there is not enough information to make a judgment, then I think the answer would be no.

DR. WANG: No, okay. It is no, we don't have enough information.

MS. BRONSTEIN: My vote is no unless more information is obtained.

DR. PINE: I guess I will make two statements. I found Dr. Temple's statement about you will look into it and, the more doubtful this diagnosis becomes, everything changes, and I would agree with that. You know, just sitting here today it has to be obvious to anybody that knows nothing about Stevens-Johnson syndrome that there is a reasonable suspicion. I think everybody would agree with that, that there is a reasonable suspicion that this was a case of Stevens-Johnson syndrome related to the medication exposure. So, that is the first thing.

The second thing is that I really don't

think it is that big a deal to cap the risk at 1/1000. So, I am going to vote no and what I would recommend is a study of 3000 patients that is not an efficacy study, that is simply designed to make sure that there is not a single case of Stevens-Johnson syndrome, you know, treated for a month.

DR. LEON: I will vote no, based on the data we have seen that modafinil has not been shown to be acceptably safe for children and adolescents with ADHD.

DR. ROBINSON: I am voting no because I think that we do need a study specifically designed to at least get a good estimate of what the rate is, and especially in a therapeutic area where modafinil hasn't shown a specific efficacy that is greater than with the already available agents.

DR. PFEFFER: I am voting no also. I think that we need more information which I think will be extremely helpful in guiding not only the clinician but enhancing perhaps compliance of patients. My feeling is that if this were approved

now, regardless of how the clinician might feel or try to explain it, I think the compliance of parents for the children would not be as good perhaps than if there were a clearer view of the risks where they could make a more informed decision. I think we need more data and I think that it is worth that wait.

DR. ARMENTEROS: Well, based on the confusion that I have been exposed to through the whole day, I am going to vote no and I am hoping that given this ADHD diagnosis we can identify readily and do studies to bring on the data. We are not talking about a condition that is rare so we should be able to move ahead at a later stage with much more clear information that in everyone's mind will be better at that stage.

DR. WELLS: Barbara Wells, and I will vote no. I don't believe the case for safety has been adequately made and, in addition, I don't believe we were convinced that it is more effective than available treatments and perhaps not as effective as available treatments. We also have reason to at

least suspect that the incidence of even the common side effects is higher with this drug than with available treatments.

MS. DOKKEN: Deborah Dokken, I also vote no on the question of safety. I mean, the uncertainty about all of this today has been almost painful and on those grounds I think we do need more information before we can put it out for the public.

DR. MALONE: I vote no also. I think that the potential population who would get the drug is fairly big, especially considering the safety risks that we have been talking about today and the apparent lack of any safety advantages for this drug.

DR. MEHTA: I know I cannot vote but if I were to vote I feel like the California voter in the presidential elections where my vote doesn't count because it has already been decided. Anyway, let me make a couple of comments. One is that I am not convinced that this is a patient with Stevens-Johnson syndrome. I have heard enough

discussions and I have been faced with and reviewed patients like that. I am not a dermatologist but still I do not believe that this is a case very clearly.

Secondly, the case for the dose relationship, that a higher dose will lead to a higher incidence of Stevens-Johnson syndrome certainly has not been made. If that is the case, then one should use as a denominator something like 3 million patients. So, we have about four or five patients with Stevens-Johnson syndrome in an exposure of 3 million people, which is no different than anything else. So, from my point of view, if I had to vote I would have voted differently with a lot of strictures about how to get more data to make sure that the real incidence is not more than what we already see.

DR. GOODMAN: Could you give us the tally?

DR. REESE: Yes. There is one yes and 12 no. Going back to question one, it was 12 yes. Dr. Andreason?

DR. ANDREASON: Just for note-taking, I

heard some discussion that a risk cap at 1/1000 would be something that you would like to know about. Did you want to talk about that or make a vote on that?

DR. PINE: Again, I would emphasize that really the question of efficacy is not on the table here, that we have been convinced of efficacy and I can imagine that a fair amount of time and energy and patients experiences have already been invested in doing that. I would not want to reinvent the wheel there. I think the main thing would be to know definitively what the risk is from a ballpark sampling. Again, just speaking for myself, if we were to see open-label treatment, treated by pediatricians who are seeing patients regularly, that there was not a single case that would raise any dermatological concerns about Stevens-Johnson syndrome in 1000 cases, then I would vote yes.

DR. REESE: Dr. Rappley?

DR. RAPPLEY: I would support that, and I think it is clear that the medication is efficacious and the comparison studies can be done

postmarketing and I would be happy with that.

DR. GOODMAN: What I am about to say is not necessarily a criticism of this particular sponsor but I think there is a lesson in here about the need for better assessment of these dermatological adverse experiences, and I think a lot of these issues would have been settled and perhaps even the outcome would have been different if we had better documentation that would have allowed our dermatological colleagues to make a more definitive conclusion. So, I think we are dealing with some fuzzy information but, given that this wasn't a compelling enough story here, both on the efficacy side and on the safety side, to reach a comfort level by which this committee could endorse this compound moving forward to market. So, I think we did err on the side of consumer protection and I would hope sincerely that the company would find the means by which it could gather the additional data to collect the necessary safety data and the outcome could be different under those circumstances.

I want to thank everybody for attending for the long day, and most of all for putting up with my scratchy voice. Thank you.

DR. LAUGHREN: And I want to thank the committee again for a heroic effort in helping us with our job. Thank you.

[Whereupon, at 4:25 p.m., the proceedings were adjourned.]

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